WEST

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L1: Entry 1 of 2 File: DWPI Jul 19, 1999

DERWENT-ACC-NO: 1999-059725
DERWENT-WEEK: 199934

TITLE: Agent for inhibiting immunoglobulin E or interleukin-5 production - comprises phthalimide derivative for treating allergies

INVENTOR: KAWASAKI, H; MIMURA, T ; SHINAGAWA, Y

PATENT-ASSIGNEE:

ASSIGNEE	CODE
JAPAN TOBACCO INC	NISB

PRIORITY-DATA: 1997JP-0147174 (May 21, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2921760 B2	July 19, 1999		088	C07D209/48
WO 9852919 A1	November 26, 1998	J	143	C07D209/48
JP 11035559 A	February 9, 1999		088	C07D209/48
AU 9874491 A	December 11, 1998		000	C07D209/48

DESIGNATED-STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS KE KG KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP 2921760B2	May 19, 1998	1998JP-0153777	
JP 2921760B2		JP11035559	Previous Publ.
WO 9852919A1	May 20, 1998	1998WO-JP02217	
JP11035559A	May 19, 1998	1998JP-0153777	
AU 9874491A	May 20, 1998	1998AU-0074491	
AU 9874491A		WO 9852919	Based on

INT-CL (IPC): A61K 31/00; A61K 31/40; A61K 31/44; A61K 31/445; A61K 31/535; C07D 209/48; C07D 401/04; C07D 401/06; C07D 401/12; C07D 403/12; C07D 405/12; C07D 409/06
ABSTRACTED-PUB-NO: JP 2921760B
EQUIVALENT-ABSTRACTS: Agent for inhibiting immunoglobulin E (IgE) or interleukin-5 (IL-5) production comprises a phthalimide derivative of formula (I) or its salt: R1-R4 = H, OH, lower alkyl, carbamoyl, alkylaminocarbonyl, carboxy, amino, NO2, halo or optionally substituted lower alkoxy or alkoxycarbonyl; A = CB1 or N; B1, B = H, cycloalkyl, aralkyl, heterocyclyl, carboxy, aralkyloxyalkyl or optionally substituted lower alkyl or aryl; or B, B1 +A = cycloalkyl or optionally substituted heterocyclyl; X = 1-4C alkylene or (CONH)p(CHR5)q; R5 = H, alkyl, aryl or aralkyl; p = 0 or 1; q = 0-2; Y = O, NR6, or S; R6 = H or lower alkyl; Z = 1-4C alkylene, 2-4C alkenylene CHR7, CONH, CO or SO2; R7 = phenyl; l-n = 0 or 1; Cy = optionally substituted aryl, cycloalkyl or heterocyclyl. (I) are new in which B = B2; A = CH or N; (X)l = (CH2)t; Y = Y1 and Z = Z1; and provided that R1-R4 are not

all H; B2 = cycloalkyl, aralkyl, heterocyclyl or optionally substituted aryl; Y1 = O, NH or S; Z1 = 1 -4C alkylene or CHR7; t = 0-4. USE - (I) inhibit IgE and IL-5 production and are useful as antiallergic agents. ADVANTAGE - (I) are selective and have efficacy with high safety.

TITLE-TERMS: AGENT INHIBIT IMMUNOGLOBULIN INTERLEUKIN PRODUCE COMPRISE PHTHALIMIDE DERIVATIVE TREAT ALLERGIC

DERWENT-CLASS: B02

CPI-CODES: B06-D03; B14-G02A; B14-L06; B14-L07;

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C1999-017561

(19)日本国特許庁（ＪＰ）　(12)特　許　公　報（Ｂ２）　(11)特許番号

第2921760号

(45)発行日　平成11年(1999)７月19日　(24)登録日　平成11年(1999)４月30日

(51)Int.Cl.[6]	識別記号	ＦＩ	
Ｃ０７Ｄ 209/48		Ｃ０７Ｄ 209/48	Ｚ
Ａ６１Ｋ 31/00	６１１	Ａ６１Ｋ 31/00	６１１
	６３７		６３７
	６４３		６４３Ｄ
31/40	６０６	31/40	６０６

請求項の数14(全 88 頁)　最終頁に続く

(21)出願番号　特願平10－153777

(22)出願日　平成10年(1998)５月19日

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(43)公開日　平成11年(1999)２月９日

審査請求日　平成10年(1998)９月11日

(31)優先権主張番号　特願平9－147174

(32)優先日　平９(1997)５月21日

(33)優先権主張国　日本（ＪＰ）

(73)特許権者　000004569
日本たばこ産業株式会社
東京都港区虎ノ門二丁目２番１号

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(74)代理人　弁理士　大東　輝雄

審査官　冨永　保

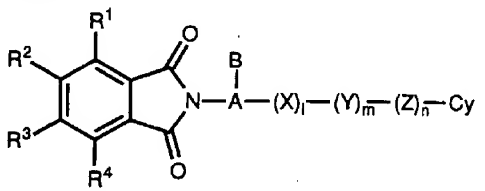
最終頁に続く

(54)【発明の名称】　フタルイミド誘導体及びそれら誘導体を含んでなる医薬

(57)【特許請求の範囲】

【請求項１】　一般式［Ｉ］

*【化１】



［Ｉ］

［式中、R^1、R^2、R^3及びR^4は同一又は異なって水素原子、水酸基、低級アルキル基、置換されてもよい低級アルコキシ基、置換されてもよいアルコキシカルボニル基、カルバモイル基、アルキルアミノカルボニル基、カルボキシ基、アミノ基、ニトロ基又はハロゲン原子を示※し；Ａは－ＣＢ[1]－（式中、B^1は水素原子、置換されてもよい低級アルキル基、シクロアルキル基、置換されてもよいアリール基、アラルキル基、複素環基、カルボキシ基又はアラルキルオキシアルキル基を示す。）又は窒素原子を示し；Ｂはシクロアルキル基、置換されてもよ

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L2: Entry 1 of 1 File: DWPI Aug 13, 1998

DERWENT-ACC-NO: 1998-446945
DERWENT-WEEK: 200171

TITLE: Compositions for delivering e.g. peptide and lipid - comprises e.g. caprylic acid or phenyl butyric acid carrier, to increase the bio-availability of the active agent

INVENTOR: GSCHNEIDNER, D; HO, K ; LEIPOLD, H R ; LEONE-BAY, A ; MILSTEIN, S J ; SARRUBI, D J ; WANG, E ; GSCHNEIDER, D ; LEIPOLD, H ; SARUBBI, D J ; WANG, E Y ; WANG, N F

PATENT-ASSIGNEE:

ASSIGNEE	CODE
EMISPHERE TECHNOLOGIES INC	EMISN

PRIORITY-DATA: 1997US-0797820 (February 7, 1997), 1997US-0796334 (February 7, 1997), 1997US-0796335 (February 7, 1997), 1997US-0796336 (February 7, 1997), 1997US-0796337 (February 7, 1997), 1997US-0796338 (February 7, 1997), 1997US-0796339 (February 7, 1997), 1997US-0796340 (February 7, 1997), 1997US-0796341 (February 7, 1997), 1997US-0797100 (February 7, 1997), 1997US-0797813 (February 7, 1997), 1997US-0797816 (February 7, 1997), 1997US-0797817 (February 7, 1997), 2000AU-0072260 (December 14, 2000), 2000AU-0072261 (December 14, 2000), 2000US-0596016 (June 16, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9834632 A1	August 13, 1998	E	147	A61K038/00
US 5804688 A	September 8, 1998		000	C07C229/00
AU 9862756 A	August 26, 1998		000	A61K038/00
US 5876710 A	March 2, 1999		000	A61K031/70
US 5879681 A	March 9, 1999		000	A61K031/70
US 5939381 A	August 17, 1999		000	A61K038/17
US 5990166 A	November 23, 1999		000	A61K009/48
EP 993831 A2	April 19, 2000	E	000	A61K047/12
US 6051561 A	April 18, 2000		000	A61K031/725
US 6060513 A	May 9, 2000		000	C07C229/34
EP 1015008 A1	July 5, 2000	E	000	A61K038/00
CA 2319672 A1	August 13, 1998	E	000	C07C235/60
CA 2319680 A1	August 13, 1998	E	000	C07C235/60
AU 200072260 A	February 22, 2001		000	A61K031/166
AU 200072261 A	February 22, 2001		000	A61K047/12
EP 1093819 A2	April 25, 2001	E	000	A61K038/29
MX 9907290 A1	May 1, 2000		000	A61K038/00
JP 2001131090 A	May 15, 2001		054	A61K045/06
US 6242495 B1	June 5, 2001		000	A01K037/18
JP 2001139494 A	May 22, 2001		054	A61K047/16
JP 2001513080 W	August 28, 2001		280	A61K047/12
NZ 337131 A	August 31, 2001		000	A61K038/00
AU 738735 B	September 27, 2001		000	A61K038/00
US 6313088 B1	November 6, 2001		000	A61K038/00

DESIGNATED-STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 9834632A1	February 6, 1998	1998WO-US02619	
US 5804688A	February 7, 1997	1997US-0796339	
AU 9862756A	February 6, 1998	1998AU-0062756	
AU 9862756A		WO 9834632	Based on
US 5876710A	February 7, 1997	1997US-0796335	
US 5879681A	February 7, 1997	1997US-0796334	
US 5939381A	February 7, 1997	1997US-0796340	
US 5990166A	February 7, 1997	1997US-0797820	
EP 993831A2	February 6, 1998	1999EP-0117292	
US 6051561A	February 7, 1997	1997US-0797813	
US 6060513A	February 7, 1997	1997US-0797817	
EP 1015008A1	February 6, 1998	1998EP-0905042	
EP 1015008A1	February 6, 1998	1998WO-US02619	
EP 1015008A1	February 6, 1998	1999EP-0117292	Related to
EP 1015008A1		EP 993831	Related to
EP 1015008A1		WO 9834632	Based on
CA 2319672A1	February 6, 1998	1998CA-2279331	Div ex
CA 2319672A1	February 6, 1998	1998CA-2319672	
CA 2319680A1	February 6, 1998	1998CA-2279331	Div ex
CA 2319680A1	February 6, 1998	1998CA-2319680	
AU 200072260A	February 6, 1998	1998AU-0062756	Div ex
AU 200072260A	December 14, 2000	2000AU-0072260	
AU 200072261A	February 6, 1998	1998AU-0062756	Div ex
AU 200072261A	December 14, 2000	2000AU-0072261	
EP 1093819A2	February 6, 1998	1998EP-0905042	Div ex
EP 1093819A2	February 6, 1998	2000EP-0122704	
EP 1093819A2		EP 1015008	Div ex
MX 9907290A1	February 6, 1998	1998WO-US02619	
MX 9907290A1	August 6, 1999	1999MX-0007290	
JP2001131090A	February 6, 1998	1998JP-0535034	Div ex
JP2001131090A	February 6, 1998	2000JP-0311231	
US 6242495B1	February 7, 1997	1997US-0797100	Cont of
US 6242495B1	June 16, 2000	2000US-0596016	
JP2001139494A	February 6, 1998	1998JP-0535034	Div ex
JP2001139494A	February 6, 1998	2000JP-0311230	
JP2001513080W	February 6, 1998	1998JP-0535034	
JP2001513080W	February 6, 1998	1998WO-US02619	
JP2001513080W		WO 9834632	Based on
NZ 337131A	February 6, 1998	1998NZ-0337131	
NZ 337131A	February 6, 1998	1998WO-US02619	
NZ 337131A		WO 9834632	Based on
AU 738735B	February 6, 1998	1998AU-0062756	
AU 738735B		AU 9862756	Previous Publ.
AU 738735B		WO 9834632	Based on
US 6313088B1	February 7, 1997	1997US-0797100	

, MX 9907290 A1 INT-CL (IPC): A01K 31/165; A01K 37/18; A01N 43/04; A61K 9/08; A61K 9/20; A61K 9/48; A61K 31/16; A61K 31/166; A61K 31/195 ; A61K 31/352; A61K 31/70; A61K 31/7052; A61K 31/725; A61K 31/726; A61K 31/727; A61K 38/00; A61K 38/04; A61K 38/11; A61K 38/17; A61K 38/21; A61K 38/22; A61K 38/23; A61K 38/27; A61K 38/28; A61K 38/29; A61K 39/00 ; A61K 39/395; A61K 45/00; A61K 45/06; A61K 47/12; A61K 47/16; A61K 47/18; A61K 47/20; A61K 47/22; A61P 5/00; A61P 5/02; A61P 5/06; A61P 5/18; A61P 31/00; A61P 43/00; C07C 229/00; C07C 229/06; C07C 229/34 ; C07C 233/00; C07C 235/52; C07C 235/60; C07C 317/14; C07D 209/02; C07D 239/02; C07D 241/02; C07D

257/04; C07D 295/18; C07D 311/04

RELATED-ACC-NO: 1996-464649;1997-549322 ;1998-387104 ;1998-398084

ABSTRACTED-PUB-NO: US 5804688A
BASIC-ABSTRACT:

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl; 2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.
ABSTRACTED-PUB-NO:

US 5876710A
EQUIVALENT-ABSTRACTS:

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl; 2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl;

2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.

US 5879681A

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl; 2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.

US 5939381A

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl; 2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.

US 5990166A

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl; 2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.

US 6051561A

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl; 2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.

US 6060513A

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl; 2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules

or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.

US 6242495B

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl; 2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.

US 6313088B

A composition comprises: (a) at least one active agent; and (b) at least one carrier selected from caprylic acid derivatives of formula X-C(=O)-NH-(CH2)7-COOH (I), phenylbutyric acid derivatives of formula (II). X = 2-aminophenyl; 2-trifluoromethoxyphenyl; 2- or 3 methoxyphenyl; 2-pyrazinyl; benzyloxy; phenoxy; 3-(2 hydroxypyridinyl); 3-(8-chromone); 4-vinylphenyl; 3,5-dimethoxy-4 hydroxyphenyl; 2-hydroxy-6-methoxyphenyl; 3-chloro-6 methoxyphenyl; 2-methoxy-4-chlorophenyl; and Y = phenyloxymethyl; pentafluorophenyl; 3-methoxyphenyl; 2 hydroxyphenyl; 2-(2,5-dimethoxycinnamoylethynyl); 2-pyrazinyl; 2 (3-carboxypyrazinyl); benzyloxy; phenoxy; chromone; 3-(2 hydroxypyridinyl); 2-, 3- or 4-iodophenyl; 2-(1-hydroxynaphthyl); 2-methoxy-4-nitrophenyl; 3-nitro-4 methoxyphenyl; 2-hydroxy-4-bromophenyl; 2-chloro-5-nitrophenyl; 2,3,5-trichlorophenyl; 2-ethoxyphenyl; 2 dimethylaminophenyl; 3-(2-chloropyridinyl).

USE - The compositions can be used to deliver biologically or chemically active agents, e.g. across the blood/brain barrier. Dosage forms may be tablets, capsules or liquids.

ADVANTAGE - The bioavailability of active agent is increased by administering the carrier compared to administration of active agent alone. The composition is particularly useful for active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone.

WO 9834632A

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: COMPOSITION DELIVER PEPTIDE LIPID COMPRISE CAPRYLIC ACID PHENYL BUTYRIC ACID CARRY INCREASE BIO AVAILABLE ACTIVE AGENT

DERWENT-CLASS: B05 P14

CPI-CODES: B04-B01B; B04-C01; B04-C02; B05-B01P; B06-A02; B06-D03; B07-H; B10-A07; B10-B02;

CHEMICAL-CODES:

Chemical Indexing M1 *01*
Fragmentation Code
M423 M431 M782 M903 N103 Q233 V735 V772 V794 V902

Chemical Indexing M2 *02*
Fragmentation Code
F012 F013 F431 G010 G011 G013 G017 G018 G019 G100
H401 H441 H541 H601 H602 H603 H609 H621 H641 H643
J0 J012 J1 J171 J3 J311 J331 J341 M121 M123
M136 M210 M211 M272 M280 M281 M311 M315 M321 M332
M342 M349 M372 M381 M391 M413 M414 M431 M510 M520
M521 M531 M532 M540 M782 M903 M904 N103 Q233 Q606
Markush Compounds
199838-JEY01-K 199838-JEY01-M

Chemical Indexing M2 *03*
Fragmentation Code
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Markush Compounds
199838-JEY02-K 199838-JEY02-M

Chemical Indexing M2 *04*
Fragmentation Code
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199838-JEY03-K 199838-JEY03-M

Chemical Indexing M2 *05*
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Q233 Q606
Markush Compounds
199838-JEY04-K 199838-JEY04-M

Chemical Indexing M2 *06*
Fragmentation Code
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K0 K3 K353 M1 M121 M147 M280 M313 M321 M332
M342 M372 M391 M414 M431 M510 M520 M532 M540 M782
M903 M904 N103 Q233 Q606
Markush Compounds
199838-JEY05-K 199838-JEY05-M

SECONDARY-ACC-NO:
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Leone-Bay et al.

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[45] **Date of Patent: Sep. 8, 1998**

[54] **COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS**

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[21] Appl. No.: **796,339**

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[51] **Int. Cl.**[6] **C07C 229/00**

[52] **U.S. Cl.** **562/444**; 252/182.31; 514/563

[58] **Field of Search** 562/444; 252/182.31; 514/563

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Attorney, Agent, or Firm—Darby & Darby

[57] **ABSTRACT**

Carrier compounds and compositions therewith which are useful in the delivery of active agents are provided. Methods of administration and preparation are provided as well.

21 Claims, No Drawings

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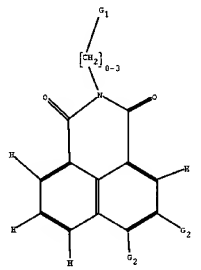

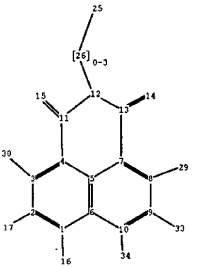

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ring bonds :
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exact/norm bonds :
4-11 7-13 9-33 10-34 11-12 11-15 12-13 13-14 25-26
exact bonds :
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normalized bonds :
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19-20 20-21 21-22 22-23
isolated ring systems :
containing 18 :

G1:CH3,OH,COOH,NH2,[*1]

G2:H,COOH,CN,NO2,X

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom
10:Atom 11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:CLASS
17:CLASS 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 25:CLASS
26:CLASS

29:CLASS 30:CLASS 33:CLASS 34:CLASS

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1 1 NAPHTHALIMIDE/CN

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L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 81-83-4 REGISTRY
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Naphthalimide (6CI, 7CI, 8CI)**
OTHER NAMES:
CN 1,8-Naphthalenedicarboximide
CN 1,8-Naphthalenedicarboxylic acid imide
CN 1,8-Naphthalimide
FS 3D CONCORD
MF C12 H7 N O2
CI COM
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, HODOC*, IFICDB, IFIPAT, IFIUDB, PIRA, PROMT, SPECINFO, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
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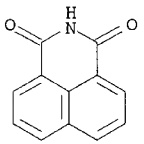

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L13 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 2000:824228 CAPLUS
DN 133:362703
TI Method of inhibiting binding of nerve growth factor to **neurotrophin** receptors using phthalimides, naphthalimides, and related compounds.
IN Ross, Gregory M.; Shamovsky, Igor L.; Marone, Sandra; Weaver, Donald F.; Riopelle, Richard J.
PA Queen's University, Can.
SO PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000069829	A1	20001123	WO 2000-CA542	20000511

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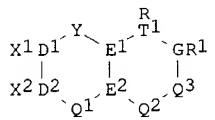
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 1999-134578 P 19990517

OS MARPAT 133:362703
GI

09/562724 Hurlick 1656



I

AB A method of inhibiting binding of nerve growth factor to the p75NTR receptor comprises contacting cells expressing this receptor with title compds. [I; D1, D2, E1, E2, G = sp2-hybridized C or N; 1 of X1, X2 H, null, the other = electroneg. atom or functional group; R, R2 = electroneg. atom or functional group; Y = N, O, S, CL, NL; L = H, alkyl, electroneg. atom or functional group; Z, Z1 = O, S, CH, CO, N, NQ; Q = alkyl, cycloalkyl, carbohydrate residue; T1, T2 = sp2- or sp3-hybridized C or N atom; R1 = mono- or polycyclic aryl, heteroaryl, monosaccharide or oligosaccharide residue, alkyl, cycloalkyl, aralkyl, alkylamino, alkoxy which is substituted with .gtoreq.1 electroneg. atom and electroneg. functional group; Q1 = (Z1)a; Q2 = Zb; Q3 = (T2R2)c; a, b, c = 0, 1; .gtoreq.1 of a, b, c = 1]. Thus, 4-carboxyphthalic anhydride and glycine were refluxed in HOAc to give 78% 4-carboxy-N-(carboxymethyl)phthalimide. The latter in PC12 cells expressing p75NTR receptors showed 116% of max. binding.

IT **26491-50-9P 202341-40-0P 254452-44-3P 295348-01-5P 307496-13-5P 307496-14-6P 307496-15-7P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(inhibitors of binding of nerve growth factor to **neurotrophin** receptors using phthalimides, naphthalimides)

RN 26491-50-9 CAPLUS
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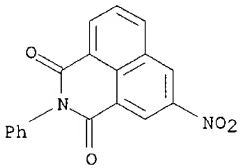

RN 202341-40-0 CAPLUS
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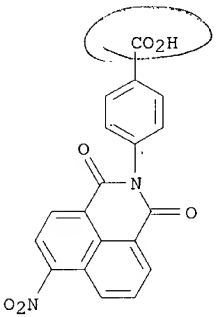

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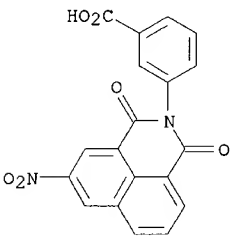

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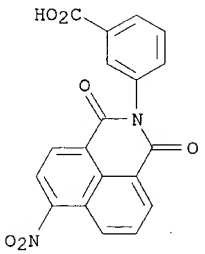

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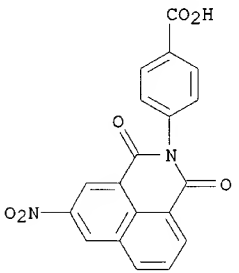
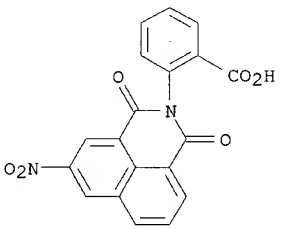
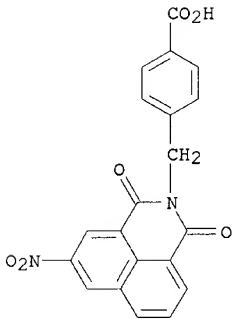


RN 307496-14-6 CAPLUS
CN Benzoic acid, 2-(5-nitro-1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)- (9CI) (CA INDEX NAME)



RN 307496-15-7 CAPLUS
CN Benzoic acid, 4-[(5-nitro-1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)methyl]- (9CI) (CA INDEX NAME)



RE.CNT 8
RE
(1) Allelix Biopharma; WO 9817278 A 1998 CAPLUS
(2) Du Pont Pharm Co; WO 0000472 A 2000 CAPLUS
(3) Gschneidner, D; WO 9834632 A 1998 CAPLUS
(4) I P A International Pharmaceut; EP 0206322 A 1986 CAPLUS
(5) Japan Tobacco Inc; WO 9852919 A 1998 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 1998:268358 CAPLUS
DN 128:317269
TI Benzoisoquinolinedione **neurotrophin** antagonist compositions and therapeutic use
IN Tehim, Ashok; Chen, Xiannong
PA Allelix Biopharmaceuticals Inc., Can.; Tehim, Ashok; Chen, Xiannong
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9817278	A1	19980430	WO 1997-CA779	19971020
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
				GB 1996-21902	A 19961021
				GB 1997-10904	A 19970527
	AU 9746968	A1	19980515	AU 1997-46968	19971020
	AU 728523	B2	20010111		
				GB 1996-21902	A 19961021
				GB 1997-10904	A 19970527
				WO 1997-CA779	W 19971020
	EP 930883	A1	19990728	EP 1997-909098	19971020
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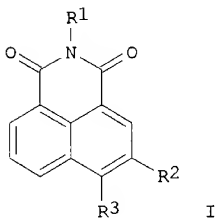
				GB 1996-21902	A 19961021

			GB 1997-10904 A 19970527
			WO 1997-CA779 W 19971020
JP 2001503397	T2	20010313	JP 1998-518756 19971020
			GB 1996-21902 A 19961021
			GB 1997-10904 A 19970527
			WO 1997-CA779 W 19971020
BR 9712424	A	20011120	BR 1997-12424 19971020
			GB 1996-21902 A 19961021
			GB 1997-10904 A 19970527
			WO 1997-CA779 W 19971020

OS MARPAT 128:317269
GI

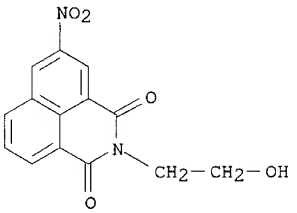


I

AB Pharmaceutical compns. comprising I (R1 = alkyl, aryl-lower alkyl, heterocyclyl-lower alkyl, etc.; R2, R3 = H, NO2, halo, di(lower alkyl)amino, cyano, etc.), or pharmaceutically acceptable salts or certain in vivo hydrolyzable esters or amides thereof, in an amt. effective to inhibit **neurotrophin**-mediated activity, and a suitable carrier, are described. The compns. are useful for inhibiting undesirable **neurotrophin**-mediated activity, e.g. the neurite outgrowth that occurs in some neurodegenerative disease states. N-[5-nitro-1H-benz[de]isoquinoline-1,3(2H)-dione]-2-aminoethanol (II) was prepd. from 3-nitro-1,8-naphthalic anhydride and 2-hydroxyethylhydrazine. II was tested for ability to inhibit neurite outgrowth, as well as in an animal model of neuropathic pain. Compds. of the invention were also tested for ability to inhibit NGF binding to P75 and TrkA.

IT **79070-65-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(benzoisoquinolinedione **neurotrophin** antagonist compns. and therapeutic use)

RN 79070-65-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-5-nitro- (9CI) (CA INDEX NAME)



IT **2382-08-3 5450-40-8 5690-46-0**
5690-46-0D, esters and amides **5810-79-7**
6917-30-2D, esters and amides **15965-03-4**
15965-03-4D, esters and amides **51411-04-2D**, esters and amides **53497-34-0 53497-34-0D**, esters and amides
69408-78-2 79070-65-8D, esters and amides
94887-57-7 100873-54-9 130001-49-9
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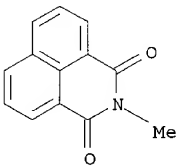
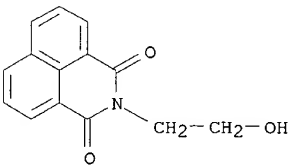
207107-66-2 207107-67-3 207107-68-4
207107-69-5 207107-70-8 207107-71-9
207107-72-0 207107-73-1 207107-74-2
207107-75-3 207107-76-4 207107-77-5
207107-78-6 207107-79-7 207107-80-0
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzoisoquinolinedione **neurotrophin** antagonist compns. and therapeutic use)

RN 2382-08-3 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-methyl- (9CI) (CA INDEX NAME)

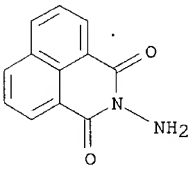


RN 5450-40-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

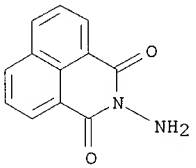


RN 5690-46-0 CAPLUS

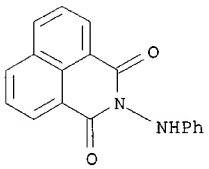
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-amino- (9CI) (CA INDEX NAME)



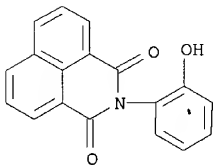
RN 5690-46-0 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-amino- (9CI) (CA INDEX NAME)



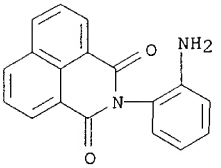
RN 5810-79-7 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(phenylamino)- (9CI) (CA INDEX NAME)



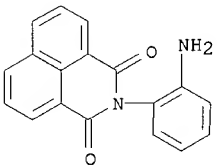
RN 6917-30-2 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyphenyl)- (9CI) (CA INDEX NAME)



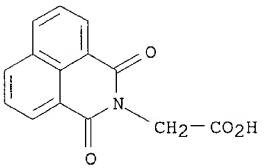
RN 15965-03-4 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminophenyl)- (9CI) (CA INDEX NAME)



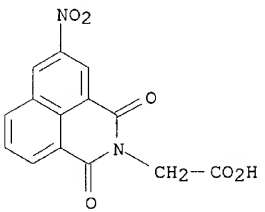
RN 15965-03-4 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminophenyl)- (9CI) (CA INDEX NAME)



RN 51411-04-2 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo- (9CI) (CA INDEX NAME)

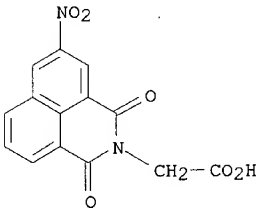


RN 53497-34-0 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 5-nitro-1,3-dioxo- (9CI) (CA INDEX NAME)

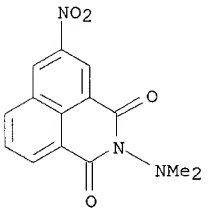


RN 53497-34-0 CAPLUS

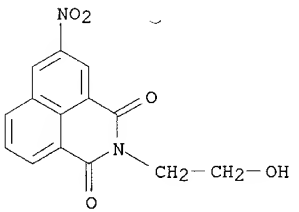
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 5-nitro-1,3-dioxo- (9CI) (CA INDEX NAME)



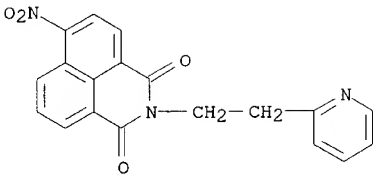
RN 69408-78-2 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(dimethylamino)-5-nitro- (9CI) (CA INDEX NAME)



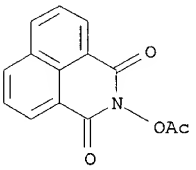
RN 79070-65-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-5-nitro- (9CI) (CA INDEX NAME)



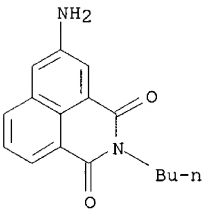
RN 94887-57-7 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-nitro-2-[2-(2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)



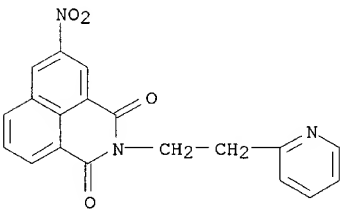
RN 100873-54-9 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(acetyloxy)- (9CI) (CA INDEX NAME)



RN 130001-49-9 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 5-amino-2-butyl- (9CI) (CA INDEX NAME)

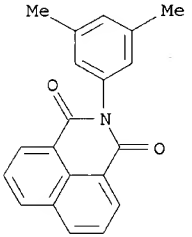


RN 162265-47-6 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 5-nitro-2-[2-(2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

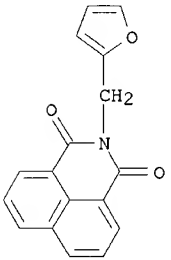


RN 194610-48-5 CAPLUS

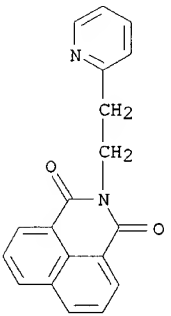
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(3,5-dimethylphenyl)- (9CI) (CA INDEX NAME)



RN 207107-62-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-furanylmethyl)- (9CI) (CA INDEX NAME)

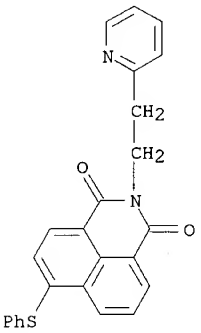


RN 207107-63-9 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-[2-(2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

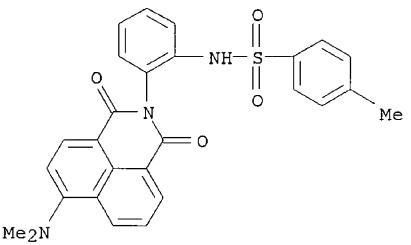


RN 207107-64-0 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-(phenylthio)-2-[2-(2-

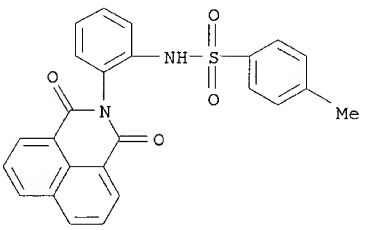
pyridinyl)ethyl]- (9CI) (CA INDEX NAME)



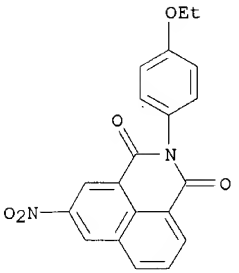
RN 207107-65-1 CAPLUS
CN Benzenesulfonamide, N-[2-[6-(dimethylamino)-1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl]phenyl]-4-methyl- (9CI) (CA INDEX NAME)



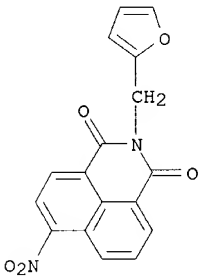
RN 207107-66-2 CAPLUS
CN Benzenesulfonamide, N-[2-(1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)phenyl]-4-methyl- (9CI) (CA INDEX NAME)



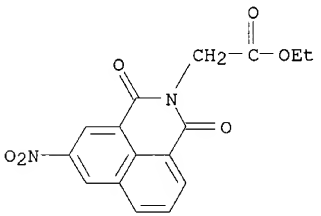
RN 207107-67-3 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 5-nitro-2-octyl- (9CI) (CA INDEX NAME)



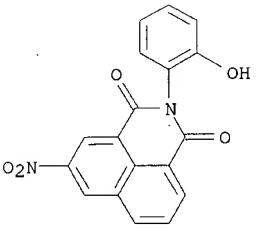
RN 207107-74-2 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-furanylmethyl)-6-nitro- (9CI) (CA INDEX NAME)



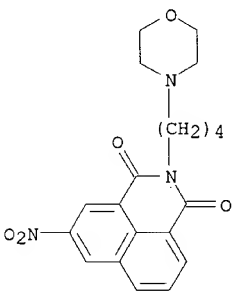
RN 207107-75-3 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 5-nitro-1,3-dioxo-, ethyl ester (9CI) (CA INDEX NAME)



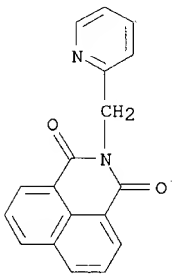
RN 207107-76-4 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyphenyl)-5-nitro- (9CI) (CA INDEX NAME)



RN 207107-77-5 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-[4-(4-morpholinyl)butyl]-5-nitro- (9CI) (CA INDEX NAME)



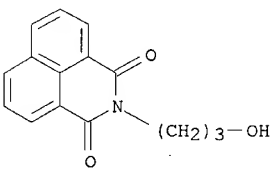
RN 207107-78-6 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-pyridinylmethyl)- (9CI) (CA INDEX NAME)



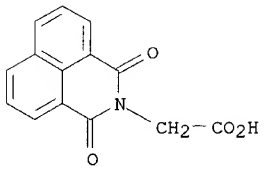
RN 207107-79-7 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-bromo-2-(dimethylamino)- (9CI) (CA INDEX NAME)

RE
(1) Armitage, B; Chem Rev 1998, V98, P1171 CAPLUS
(2) Armitage, B; J Am Chem Soc 1994, V116, P9847 CAPLUS
(3) Aveline, B; J Am Chem Soc 1997, V119, P11785 CAPLUS
(4) Barrette, W; Anal Chem 1984, V56, P1890 CAPLUS
(5) Breslin, D; J Am Chem Soc 1996, V118, P2311 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

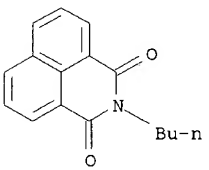
L17 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1996:89778 CAPLUS
DN 124:225399
TI Use of 3-(1,8-naphthalimido)propyl-modified silyl silica gel as a stationary phase for the high-performance liquid chromatographic separation of purine derivatives
AU Nakashima, Kenichiro; Inoue, Keiko; Mayahara, Kumiko; Kuroda, Naotaka; Hamachi, Yozo; Akiyama, Shuzo
CS School of Pharmaceutical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki, 852, Japan
SO J. Chromatogr., A (1996), 722(1 + 2), 107-13
CODEN: JCRAEY; ISSN: 0021-9673
DT Journal
LA English
AB The use of a packing material, 3-(1,8-naphthalimido)propyl-modified silyl silica gel (NAIP), as a stationary phase for HPLC, has been studied. NAIP behaved like a reversed-phase stationary phase with some .vpi.-.vpi. interaction. Purine derivs., i.e., xanthine, hypoxanthine, uric acid, theobromine, theophylline and caffeine, were sepd. by a column packed with NAIP using an eluent of borate soln. (pH 6.4)-MeOH (50:50, vol./vol.). Of these, caffeine was selected as the target of the subsequent investigation and its detn. was examd. in com. available medicinal drinks and **pharmaceutical** prepns. The av. recoveries of caffeine were 98.0-107.4% for five drinks and 99.6-107.8% for five tablets and one powder. Subsequently, detn. of caffeine and its metabolites in human plasma was examd. In twelve normal human plasma, caffeine levels ranged from 0.24 to 4.26 .mu.g/mL. Time curves of plasma caffeine concns. and those of its demethylated metabolite, 1,7-dimethylxanthine (1,7-DMX), after an oral ingestion of caffeine (200 mg) were measured by the proposed method and it was found that the max. concns. of caffeine and 1,7-DMX were obtained at 1-1.5 h and 3-6 h after ingestion, resp.
IT **6914-97-2D**, silica gel reaction product
RL: DEV (Device component use); USES (Uses)
(3-(1,8-naphthalimido)propyl-modified silyl silica gel as a stationary phase for the HPLC sepn. of purine derivs.)
RN 6914-97-2 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(3-hydroxypropyl)- (9CI) (CA INDEX NAME)



L17 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS


O
N
CH2—CO2H
O

L29 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 2001:580580 CAPLUS
DN 135:352331
TI Targeting of human Tmolt4 leukemic type II IMP dehydrogenase by cyclic imide related derivatives
AU Hall, Iris H.; Barnes, Betsy Jo; Ward, E. Stacy; Wheaton, Jessica R.; Shaffer, Kara A.; Cho, Sue E.; Warren, Amy E.
CS Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, NC, 27599-7360, USA
SO Arch. Pharm. (Weinheim, Ger.) (2001), 334(7), 229-234
CODEN: ARPMAS; ISSN: 0365-6233
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
AB 2,3-Dihydrophthalazine-1,4-diones, indazolones, 3-imino-1-oxoisodolines, homophthalimides, naphthalidimides, diphenamides, and 6,7-dihydro-5H-dibenz[c,e]azepines proved to be potent inhibitors of the activity of human Tmolt4 T cell leukemia type II IMP dehydrogenase (IMPDH). This inhibition was competitive, yielding Ki values in the range of 1.96 to 48.9 .mu.M. The inhibition of type II IMPDH correlated pos. with the inhibition of the growth of Tmolt4 cells, the syntheses of DNA and purine, and the activity of crude IMPDH. The type II IMPDH isoform is found in rapidly proliferating cells. The isoform present in normal resting cells, type I IMPDH, was elevated by the compds. at 100 .mu.M. In addn., compd. 5 significantly increased the type I enzyme activity in a concn. and time dependent manner. The selectivity of these derivs. towards type II IMPDH will allow for the sepn. of cellular effects, which should reduce clin. toxicity when treating with antimetabolite IMPDH inhibitors.
IT **6914-62-1**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting of human Tmolt4 leukemic type II IMPDH by cyclic imide related derivs.)
RN 6914-62-1 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-butyl- (9CI) (CA INDEX NAME)

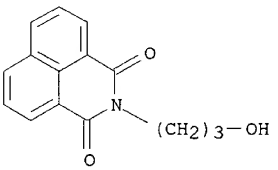


RE.CNT 22
RE
(4) Cadman, E; J Biol Chem 1981, V256, P1695 CAPLUS
(5) Dayton, J; J Immunol 1994, V152, P984 CAPLUS
(7) Hager, P; Biochem Pharmacol 1995, V49, P1323 CAPLUS
(8) Hall, I; Anti-Cancer Res 1994, V14, P2053 CAPLUS
(9) Hall, I; AntiCancer Drugs 1992, V3, P55 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 2000:496121 CAPLUS
DN 133:266702

09758917

TI The synthesis and in vitro cytotoxic studies of novel bis-naphthalimidopropyl polyamine derivatives
AU Lin, P. K. T.; Pavlov, V. A.
CS School of Applied Sciences, The Robert Gordon University, Aberdeen, AB25 1HG, UK
SO Bioorg. Med. Chem. Lett. (2000), 10(14), 1609-1612
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 133:266702
AB Bis-naphthalimidopropyl putrescine (BNIPPut), spermidine (BNIPSpd), spermine (BNIPSpm) and oxa-putrescine (BNIPOPut) were synthesized and their growth-inhibitory properties characterized. All these compds. except for BNIPOPut, showed high in vitro cytotoxic activity (with mean GI50 values between 0.5 and 8.45 .mu.M) and selectivity against cancer cells derived from nine different human tumors. The increased content of nitrogen atoms in the linker chain of BNIPSpd and BNIPSpm significantly improved their aq. dissoln. properties with a marginal decrease in their cytotoxic activity.
IT **6914-97-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction with tosyl chloride)
RN 6914-97-2 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(3-hydroxypropyl)- (9CI) (CA INDEX NAME)



RE.CNT 10
RE
(1) Bailly, C; Eur J Biochem 1996, V240, P195 CAPLUS
(2) Bousquet, P; Cancer Res 1995, V55, P1176 CAPLUS
(3) Brana, M; Anticancer Drug Des 1993, V8, P257 CAPLUS
(4) Brana, M; Cancer Chemother Pharmacol 1980, V4, P61 CAPLUS
(5) Brana, M; Eur J Med Chem 1995, V30, P235 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 2000:34858 CAPLUS
DN 132:93221
TI Preparation of naphthalimidobenzamide derivatives as **antitumor** agents
IN Noguchi, Kazuharu; Wakida, Motoji; Suzuki, Kenji; Yamada, Yuji; Asao, Tetsuji
PA Taiho Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000001672	A1	20000113	WO 1999-JP3574	19990702
	W: AU, CA, JP, KR, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
				JP 1998-189078 A	19980703
	AU 9943963	A1	20000124	AU 1999-43963	19990702
	AU 727591	B2	20001214		
				JP 1998-189078 A	19980703
				WO 1999-JP3574 W	19990702
	EP 1020446	A1	20000719	EP 1999-926895	19990702
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
				JP 1998-189078 A	19980703
				WO 1999-JP3574 W	19990702
	US 6300331	B1	20011009	US 2000-508044	20000303
				JP 1998-189078 A	19980703
				WO 1999-JP3574 W	19990702

OS MARPAT 132:93221

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB 2-(3-Carbamoylphenyl)-1H-benz[de]isoquinoline-1,3(2H)-dione derivs. represented by general formula (I) or salts thereof (wherein R1 is hydrogen,NO2, OH, NH2, halo, cyano, CO2H, CONH2, ureido, alkyl, trihaloalkyl, alkoxy, etc.; Y is hydrogen or -CON(R4)-A2-X2; R2 and R4 are each independently hydrogen or alkyl; A1 and A2 are each independently linear or branched alkylene which may be interrupted by N(R3), O, S, CONH, NHCO, S(O), or SO2 (wherein R3 is hydrogen or the like); X1 is optionally substituted aryl, heteroaryl, aryldicarbonylimino, heteroaryldicarbonylimino, arylamino, heteroarylamino, arylcarbonylamino, etc.; and X2 is H, optionally substituted aryl, heterocyclyl, aryldicarbonylimino, heteroaryldicarbonylimino, arylamino, heteroarylamino, arylcarbamoyl, etc.; m = 1-3), which exhibit high affinity for DNA, are prepd. Thus, a suspension of 711 mg 1-[N-[2-[(2-aminoethyl)amino]ethyl]carbamoyl]-3-(3-nitro-1,8-naphthalimido)-5-[N-(2-piperidinoethyl)carbamoyl]benzene hydrochloride, 0.5 mL Et3N, and 243 mg 3-nitro-1,8-naphthalic anhydride in 4 mL DMF was stirred at 60.degree. for 30 min to give 72.2% title compd. (II.HCl). II.HCl in vivo inhibited the proliferation of human melanoma LOX, human pancreatic cancer PAN, human breast cancer MX1, and human stomach cancer AZ521 cells transplanted s.c. in nude mice by 96.2, 59.8, 71.8, and 79.5%, resp.

IT **254451-70-2P 254451-72-4P 254451-74-6P**
254451-75-7P 254451-76-8P 254451-77-9P
254451-78-0P 254451-79-1P 254451-80-4P
254451-81-5P 254451-82-6P 254451-83-7P
254451-84-8P 254451-86-0P 254451-87-1P
254451-88-2P 254451-89-3P 254451-90-6P
254451-91-7P 254451-92-8P 254451-93-9P
254451-94-0P 254451-95-1P 254451-96-2P
254451-97-3P 254451-98-4P 254451-99-5P
254452-00-1P 254452-01-2P 254452-02-3P
254452-03-4P 254452-04-5P 254452-05-6P
254452-06-7P 254452-07-8P 254452-08-9P

254452-10-3P 254452-11-4P 254452-12-5P
254452-13-6P 254452-14-7P 254452-15-8P
254452-16-9P 254452-17-0P 254452-18-1P
254452-19-2P 254452-20-5P 254452-21-6P
254452-22-7P 254452-23-8P 254452-24-9P
254452-25-0P 254452-26-1P 254452-27-2P
254452-28-3P 254452-29-4P 254452-30-7P
254452-58-9P 254453-06-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of naphthalimidobenzamide derivs. as **antitumor** agents)

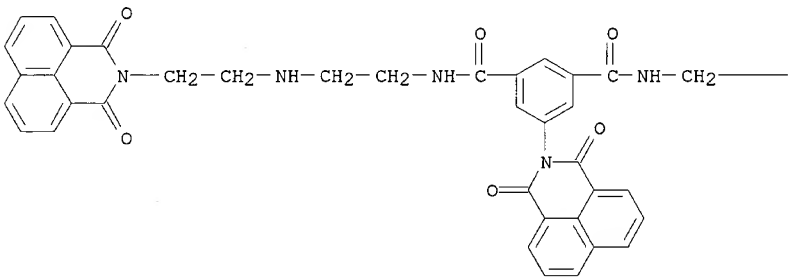
RN 254451-70-2 CAPLUS

CN 1,3-Benzenedicarboxamide, 5-(1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)-N,N'-bis[2-[[2-(1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)ethyl]amino]ethyl]-, dimethanesulfonate (9CI) (CA INDEX NAME)

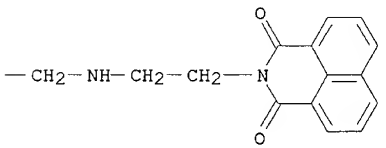
CM 1

CRN 254451-69-9
CMF C52 H41 N7 O8

PAGE 1-A

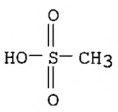


PAGE 1-B

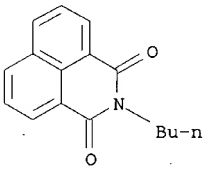


CM 2

CRN 75-75-2
CMF C H4 O3 S

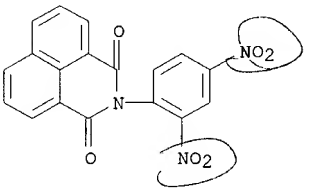


RN 6914-62-1 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-butyl- (9CI) (CA INDEX NAME)

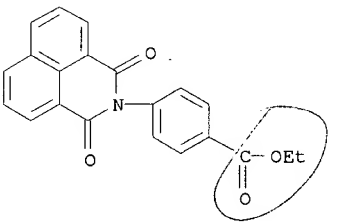


IT **94210-30-7 94887-62-4**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antitumor** activity of, structure in relation to, computer assisted evaln. of)

RN 94210-30-7 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)



RN 94887-62-4 CAPLUS
CN Benzoic acid, 4-(1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)-, ethyl ester (9CI) (CA INDEX NAME)

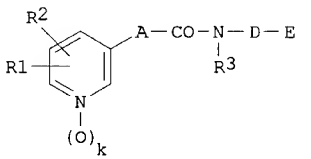


> d 1-2 fbib abs hitstr

L31 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 1999:404952 CAPLUS
DN 131:58758
TI Cyclic imide-substituted pyridylalkanecarboxamides, pyridylalkenecarboxamides and pyridylalkynecarboxamides useful as **cytostatic** and immunosuppressive agents
IN Biedermann, Elfi; Hasmann, Max; Loser, Roland; Rattel, Benno; Reiter, Friedemann; Schein, Barbara; Seibel, Klaus; Vogt, Klaus; Wosikowski, Katja
PA Klinge Pharma G.m.b.H., Germany
SO PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9931087	A1	19990624	WO 1998-EP8267	19981216
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
			DE 1997-19756212A	19971217
DE 19756212	A1	19990701	DE 1997-19756212	19971217
ZA 9811231	A	19990608	ZA 1998-11231	19981208
			DE 1997-19756212A	19971217
AU 9924146	A1	19990705	AU 1999-24146	19981216
			DE 1997-19756212A	19971217
			WO 1998-EP8267 W	19981216
EP 1042315	A1	20001011	EP 1998-966634	19981216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
			DE 1997-19756212A	19971217
			WO 1998-EP8267 W	19981216

OS MARPAT 131:58758
GI



I

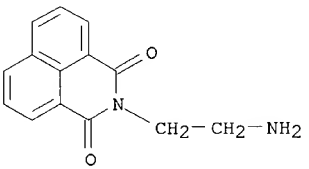
AB Pyridine derivs. I [R1 = H, OH, halo, CN, or org. group; R2 = H, halo, CN, alkyl, trifluoromethyl, OH, alkoxy, or aralkoxy; R3 = H, alkyl, alkenyl, alkynyl, OH, alkoxy, or aryloxy; A = (substituted) alkylene, 1,2-cyclopropylene, (substituted) alkenylene, (substituted) alkadienylene, (substituted) hexatrienylene, or ethynylene; D = (substituted) alkylene,

(substituted) alkenylene, (substituted) alkynylene (in which 1-3 CH2 units is isosterically replaced by O, S, NR4, CO, SO, or SO2, R4 = H, alkyl, alkenyl, acyl, or alkanesulfonyl); E = N-substituted cyclic imide or N-substituted cyclic sulfonimide; k = 0 or 1] are manufd. for use as **cytostatic** agents and immunosuppressive agents. Thus, slowing adding 46.9 mmol oxalyl chloride to 20 mmol 3-(3-pyridyl)acrylic acid suspended in CH2Cl2, stirring the mixt. with ice-cooling for 30 min and then at room temp. overnight, suspending the resulting acid chloride in CH2Cl2, cooling to 0.degree. under anhyd. conditions, adding 17.6 mmol 4-(2,5-dioxo-3,4-diphenyl-2,5-dihydropyrrol-1-yl)butylamine-HCl in CH2Cl2 and 39.5 mmol Et3N dropwise, and stirring an addnl. 2 h at room temp. gave N-[4-(2,5-dioxo-3,4-diphenyl-2,5-dihydropyrrol-1-yl)butyl]-3-pyridin-3-ylacrylamide.

IT **162265-51-2P**
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation)
(cyclic imide-substituted pyridyl carboxamides for **cytostatic** and immunosuppressive agents)

RN 162265-51-2 CAPLUS

CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminoethyl)- (9CI) (CA INDEX NAME)



RE.CNT 2

RE

(1) BYK Gulden Lomberg Chem FAB; WO 9115485 A 1991 CAPLUS

(2) Takeda Chemical Industries Ltd; EP 0522606 A 1993 CAPLUS

L31 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS

AN 1981:532639 CAPLUS

DN 95:132639

TI Synthesis and **cytostatic** activity of benz[de]isoquinoline-1,3-diones. Structure-activity relationships

AU Brana, Miguel Fernandez; Sanz, Antonio Martinez; Castellano, Jose Maria; Roldan, Cristobal Martinez; Roldan, Cristina

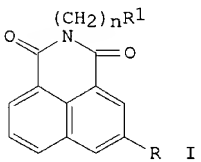
CS Fac. Cienc. Quim., Univ. Complutense, Madrid, Spain

SO Eur. J. Med. Chem. - Chim. Ther. (1981), 16(3), 207-12
CODEN: EJMCA5; ISSN: 0009-4374

DT Journal

LA English

GI

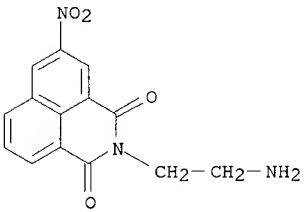


I

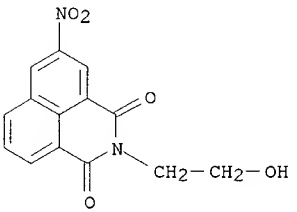
AB Fifty-one isoquinolinediones I (R = NO2, NH2, Cl, OH, NHCO2Et, MeO, NHAc, H, CMe3; R1 = NMe2, NEt2, pyrrolidino, piperidino, morpholino, 1-ethyl-3-piperidino, 4-methyl-1-piperazinyl, etc.) were prepd. in 11-95% yield. Thus, reaction of 3-nitro-1,8-naphthalic anhydride and H2N(CH2)2NMe2 gave 64% I (R = NO2, R1 = NMe2, n = 2). The biol. activity was max. (inhibiting the growth of HeLa cells) when n = 2. The presence of terminal N is essential for **cytostatic** activity. Substitution of polar atoms, e.g., S or O, decreased the cytotoxic activity.

IT **79070-63-6P 79070-65-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and **cytostatic** activity of, structure in relation to)

RN 79070-63-6 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminoethyl)-5-nitro- (9CI) (CA INDEX NAME)



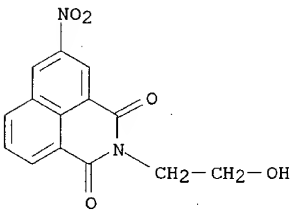
RN 79070-65-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-5-nitro- (9CI) (CA INDEX NAME)



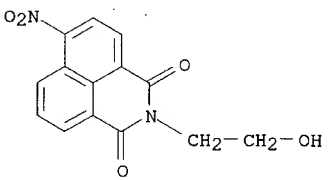
cumulative with 5/7 Miller

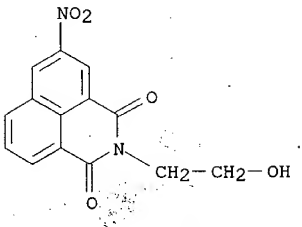
09758917

DN 115:67772
TI Fluorescent markers for hypoxic cells: a study of novel heterocyclic compounds that undergo bioreductive binding
AU Hodgkiss, R. J.; Begg, A. C.; Middleton, R. W.; Parrick, J.; Stratford, M. R. L.; Wardman, P.; Wilson, G. D.
CS Gray Lab. Cancer Res., Mt. Vernon Hosp., Northwood/Middlesex, HA6 2JR, UK
SO Biochem. Pharmacol. (1991), 41(4), 533-41
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB The bioreductive metab. and binding of nitroarom. compds. has been suggested as a method for the identification of hypoxic **tumor** cells. Bound metabolites of suitable nitroaryl compds. (and some other reducible arom. compds.) may fluoresce, offering an alternative to radiolabeling or NMR, etc., as a diagnostic method. In this study the synthesis of some heteroarom. nitro compds. is given together with the results obtained from testing of these and other mainly nitro arom. compds. in vitro as potential bioreductive fluorescent probes for hypoxic cells in tumors. Compds. were incubated with oxygenated or hypoxic mammalian cell suspensions for various times before evaluation of the cellular fluorescence from bioreductive metabolites by fluorescence microscopy and flow cytometry. Among those compds. yielding fluorescent metabolites in cells, considerable variation in hypoxic-to-oxic differential fluorescence was obsd. The in vitro mammalian cell test system showed several of the compds. to be sufficiently promising to merit further investigation in vivo.
IT **79070-65-8 92060-89-4**
RL: ANST (Analytical study)
(fluorescent marker, for hypoxic **tumor** cells)
RN 79070-65-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-5-nitro- (9CI) (CA INDEX NAME)

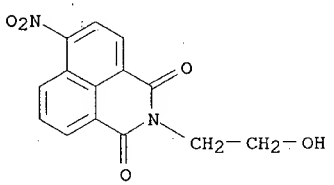


RN 92060-89-4 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-6-nitro- (9CI) (CA INDEX NAME)

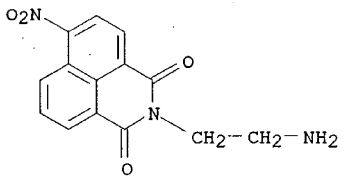




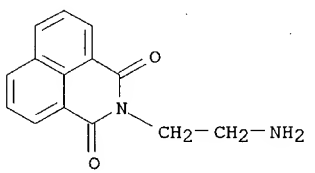
RN 92060-89-4 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-6-nitro- (9CI) (CA INDEX NAME)



RN 162265-48-7 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminoethyl)-6-nitro- (9CI) (CA INDEX NAME)



RN 162265-51-2 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminoethyl)- (9CI) (CA INDEX NAME)



L29 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1991:467772 CAPLUS

analogs

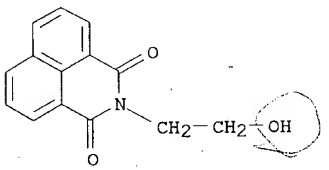
AU Miller, Kelli E.; Grace, James M.; Macdonald, Timothy L.
CS Dep. Chem., Univ. Virginia, Charlottesville, VA, 22901, USA

SO Bioorg. Med. Chem. Lett. (1994), 4(13), 1643-5
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English

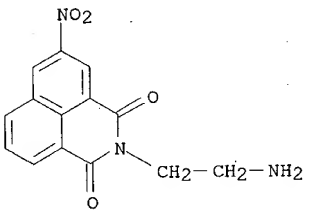
AB Amonafide (4-aminobenzoisoquinolinedione) and its structural analog, mitonafide, have been shown to stabilize topoisomerase II cleavable complexes. The position of the nitro group and structural modifications of the side chain influence the interactions between drug, enzyme, and DNA. It was shown that the analogs with the nitro in the 5-position are the most potent inhibitors in this structural class.

IT **5450-40-8P 79070-63-6P 79070-65-8P**
92060-89-4P 162265-48-7P 162265-51-2P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mitonafide analog, as **antitumor** agent; stabilization of DNA topoisomerase II-DNA cleavable complex by mitonafide analogs)

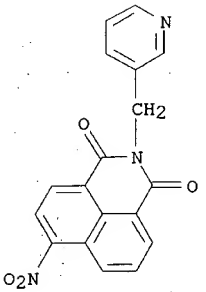
RN 5450-40-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)



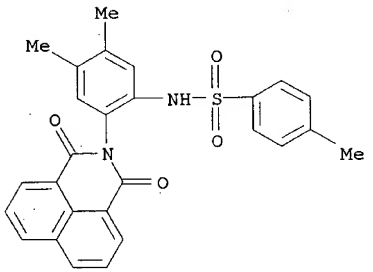
RN 79070-63-6 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminoethyl)-5-nitro- (9CI) (CA INDEX NAME)



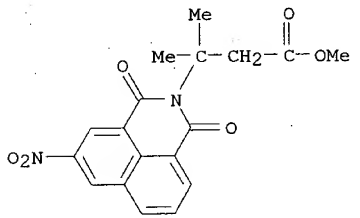
RN 79070-65-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-5-nitro- (9CI) (CA INDEX NAME)



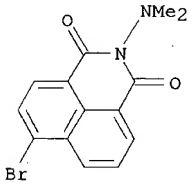
RN 207107-71-9 CAPLUS
CN Benzenesulfonamide, N-[2-(1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)-4,5-dimethylphenyl]-4-methyl- (9CI) (CA INDEX NAME)



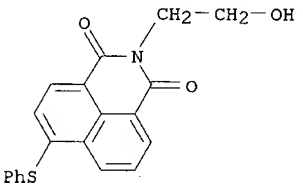
RN 207107-72-0 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-propanoic acid, .beta.,.beta.-dimethyl-5-nitro-1,3-dioxo-, methyl ester (9CI) (CA INDEX NAME)



RN 207107-73-1 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(4-ethoxyphenyl)-5-nitro- (9CI) (CA INDEX NAME)



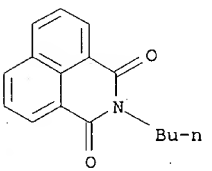
RN 207107-80-0 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-6-(phenylthio)-(9CI) (CA INDEX NAME)



09758917

=> d 1-8 fbib abs hitstr

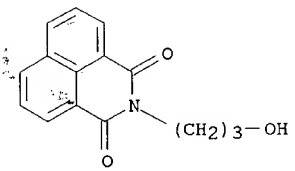
L17 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1999:331957 CAPLUS
DN 131:78991
TI Solubilization of 1,4,5,8-naphthalenediimides and 1,8-naphthalimides through the formation of novel host-guest complexes with .alpha.-cyclodextrin
AU Brochsztain, Sergio; Politi, Mario J.
CS Laboratorio Interdepartamental de Cinetica Rapida Departamento de Bioquimica Instituto de Quimica, Universidade de Sao Paulo, Sao Paulo, 05599-970, Brazil
SO Langmuir (1999), 15(13), 4486-4494
CODEN: LANGD5; ISSN: 0743-7463
PB American Chemical Society
DT Journal
LA English
AB The solubilities of 1,8-naphthalimides and 1,4,5,8-naphthalenediimides in water were studied. A large soly. increase was found for N-butyl-1,8-naphthalimide (MBN) and N,N'-dibutyl-1,4,5,8-naphthalenediimide (DBN) in the presence of .alpha.-cyclodextrin (.alpha.-CD), indicating the formation of inclusion complexes. The presence of the N-Bu group is required for complex formation; the Bu groups are the binding sites for .alpha.-CD. Soly. isotherms for the systems MBN/.alpha.-CD and DBN/.alpha.-CD show the presence of 1:1 complexes for the former and of both 1:1 and 1:2 complexes for the latter. Assocn. consts. of K = 470 M-1 for the MBN/.alpha.-CD complex, K11 = 1316 M-1 and K12 = 329 M-1 for the stepwise assocn. consts. in the DBN/.alpha.-CD system were estd. MBN undergoes hydrolysis in water, which is inhibited by the complexation with .alpha.-CD. The remarkable solubilization in water and stabilization toward hydrolysis makes these novel complexes of imides and diimides with .alpha.-CD potentially useful in the **pharmaceutical** applications known for these imides, as well as in the prepn. of new materials, like polyimide-based polyrotaxanes.
IT **6914-62-1**
RL: PEP (Physical, engineering or chemical process); RCT (Reactant); PROC (Process)
(solubilization in water of 1,4,5,8-naphthalenediimides and 1,8-naphthalimides through formation of complexes with .alpha.-cyclodextrin)
RN 6914-62-1 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-butyl- (9CI) (CA INDEX NAME)



RE.CNT 72
RE
(1) Adachi, M; J Phys Chem 1995, V99, P14240 CAPLUS
(2) Alexiou, M; J Chem Soc Perkin Trans 2 1990, P837 CAPLUS
(3) Asahi, T; Bull Chem Soc Jpn 1998, V71, P1277 CAPLUS

(4) Aveline, B; J Am Chem Soc 1997, V119, P11785 CAPLUS
(6) Barros, T; J Photochem Photobiol A: Chem 1993, V76, P55 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1999:234509 CAPLUS
DN 131:29312
TI Nucleic Acid Oxidation Mediated by Naphthalene and Benzophenone Imide and Diimide Derivatives: Consequences for DNA Redox Chemistry
AU Rogers, Joy E.; Kelly, Lisa A.
CS Department of Chemistry and Biochemistry, University of Maryland Baltimore County, Baltimore, MD, 21250, USA
SO J. Am. Chem. Soc. (1999), 121(16), 3854-3861
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB The rate consts. for electron transfer from GMP, AMP, CMP, and thymidine 5'-monophosphate (TMP) to the triplet excited states of N-(3-propanol)-1,8-naphthalimide (NI), N,N'-(3-propanol)-1,4,5,8-naphthaldiimide (NDI), and N,N'-(3-propanol)-3,3',4,4'-benzophenonediimide (BPDI) have been detd. in 1:1 H2O/CH3CN soln. Upon 355-nm (8 ns) laser flash excitation of each of the imide or diimides in soln., the triplet states decayed by first-order kinetics under conditions of low excitation energy. Photoinduced electron transfer to the lowest electronically excited triplet state of N-(3-propanol)-1,8-naphthalimide from GMP occurred with a rate const. of 2.0 .times. 107 M-1 s-1. Electron-transfer quenching by the other nucleotides was almost 2 orders of magnitude slower. In the case of BPDI, photooxidn. rate consts. ranged from 2.3 .times. 108 M-1 s-1 for quenching by CMP to 1.1 .times. 109 M-1 s-1 by GMP. In all cases, the imide radical anion was obsd. by laser flash photolysis, and the yields were quantified. From these investigations, nucleotide oxidn. by the triplet state of a series of redox-active photosensitizers has been demonstrated. The results represent a systematic study of nucleotide oxidn. by the triplet states of a series of structurally related org. photosensitizers in which the redn. potential can be tuned by ca. 800 mV. The greater than 100-fold variation in bimol. rate consts. for oxidn. of base monophosphates by these photosensitizers offers the prospect of kinetic "selectivity" of oxidative damage in random-sequence DNA.
IT **6914-97-2**
RL: RCT (Reactant)
(nucleic acid oxidn. mediated by naphthalene and benzophenone imide and diimide derivs.: consequences for DNA redox chem.)
RN 6914-97-2 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(3-hydroxypropyl)- (9CI) (CA INDEX NAME)

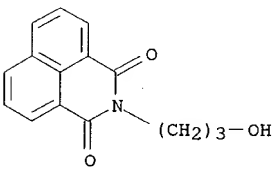


RE.CNT 34

AN 1995:743031 CAPLUS
DN 123:123211
TI Phosphorus compounds as endothelin-converting enzyme inhibitors
IN Elliott, John Duncan; Lee, Chao-Pin
PA Smithkline Beecham Corp., USA
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9513817	A1	19950526	WO 1994-US13374	19941116
	W: JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
				US 1993-154233	19931118

OS MARPAT 123:123211
AB Novel phosphorus compds. are described which are endothelin-converting enzyme inhibitors. The compds. are useful for the treatment of hypertension, renal failure or cerebrovascular disease. Examples of inhalant, tablet, and parenteral formulations of endothelin-converting enzyme inhibitors are given.
IT **6914-97-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and formulation of phosphorus compds. as endothelin-converting enzyme inhibitors)
RN 6914-97-2 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(3-hydroxypropyl)- (9CI) (CA INDEX NAME)



L17 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1993:610735 CAPLUS
DN 119:210735
TI **Pharmaceutical** compositions for treatment of diabetic neuropathies
IN Groenhout, Cornelis Martinus
PA AKZO N. V., Neth.
SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9315752	A1	19930819	WO 1993-EP345	19930212
	W: AU, CA, FI, JP, KR, NO, NZ, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

				EP 1992-200440	19920217
AU 9334970	A1	19930903		AU 1993-34970	19930212
				EP 1992-200440	19920217
				WO 1993-EP345	19930212

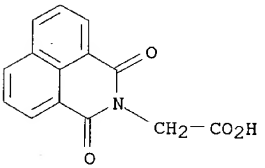
OS MARPAT 119:210735

AB **Pharmaceutical** compns. contg. an aldose reductase inhibitor, e.g. tolrestat (I), and a hexapeptide H-Me(X)-Glu-His-Phe-D-Lys-Phe-Y [Met(X)=MetO, MetO2; Y=Gly-Z, Z; Z=OH, esterified OH, NH2] are useful for the treatment and prevention of diabetic neuropathies. An injection soln. contained H-MeO2-Glu-His-Phe-D-Lys-PheOH 3.0, Me p-hydroxybenzoate 1.0, Na acetate.cntdot.3H2O 1.4, NaCl 7, and water q.s. 1mL, pH=<6.0. An injection and a tablet contg. 200mg I are administered/day.

IT **51411-04-2**, Alrestatin
RL: BIOL (Biological study)
(**pharmaceutical** compns. contg., for treatment of diabetic neuropathies in combination with hexapeptides)

RN 51411-04-2 CAPLUS

CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo- (9CI) (CA INDEX NAME)



L17 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS

AN 1989:586817 CAPLUS

DN 111:186817

TI Test models to determine potential ocular drug induced side effects

AU Lerman, Sidney

CS Eye Res. Lab., New York Med. Coll., Valhalla, NY, 10595, USA

SO Lens Eye Toxic. Res. (1989), 6(1-2), 1-36
CODEN: LETRET; ISSN: 1042-6922

DT Journal

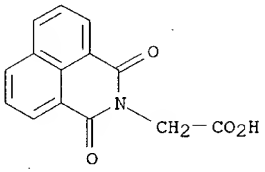
LA English

AB A discussion is presented of various methods valuable in detecting the toxicity and pharmacol. activity of ocular drugs. Fluorescence and phosphorescence spectroscopy are rapid and noninvasive techniques for monitoring certain compds. within the ocular lens. Raman spectroscopy is useful for the evaluation of SH and SS concns. in the ocular lens and can be correlated with concomitant biochem. studies employing the Elman reaction. NMR spectroscopy is useful in detg. organophosphate levels in lens, reflecting the state of normal viability of the lens during incubation with ocular drugs. Proton NMR imaging and NMR T1 and T2 pulse relaxation studies may be valuable in studying the efficacy of anti-cataract drugs. Liposomal drug delivery systems for ocular drugs are also discussed.

IT **51411-04-2**
RL: PROC (Process)
(in eye, spectroscopy in study of)

RN 51411-04-2 CAPLUS

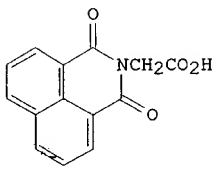
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo- (9CI) (CA INDEX NAME)



L17 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1979:192561 CAPLUS
DN 90:192561
TI Eye drops containing 1,3-dioxo-1H-benzo[d,e]isoquinoline-2(3H)-acetic acid
PA American Home Products Corp., USA
SO Jpn. Kokai Tokkyo Koho, 2 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 54028810	A2	19790303	JP 1977-139395	19771119
				US 1977-821051	19770801
	GB 2001529	A	19790207	GB 1978-31226	19780726
	GB 2001529	B2	19820616		
				US 1977-821051	19770801
	ZA 7804247	A	19800227	ZA 1978-4247	19780726
				US 1977-821051	19770801
	BE 869384	A1	19790129	BE 1978-189599	19780728
				US 1977-821051	19770801
	AT 7805516	A	19800715	AT 1978-5516	19780728
	AT 361124	B	19810225		
				US 1977-821051	19770801
	FR 2399249	A1	19790302	FR 1978-22648	19780731
				US 1977-821051	19770801
	ES 472892	A1	19791016	ES 1978-472892	19780731
				US 1977-821051	19770801
	AU 7838465	A1	19800207	AU 1978-38465	19780731
				US 1977-821051	19770801

GI



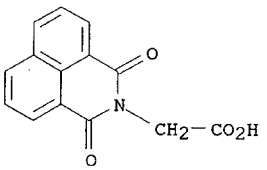
I

AB Eye drops contain 1,3-dioxo-1H-benzo[d,e]isoquinoline-2(3H)-acetic acid (I) [**51411-04-2**] or its **pharmaceutical** salts as active ingredient and hydroxyethyl cellulose (II) [9004-62-0], with pH

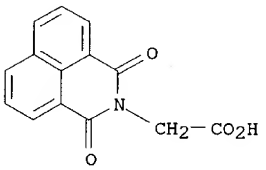
adjusted to .apprx.6. II promotes the absorption of I. Thus, an eye lotion was prepd. contg. I 12 , II 1.5, KOH 3.25 g, 17% benzalkonium chloride 0.06 mL, EDTA 0.1 g and H2O to 100 mL (pH adjusted to 6 with HCl).

IT **51411-04-2 51411-04-2D**, salts
RL: BIOL (Biological study)
(eye drops contg. hydroxyethyl cellulose and)

RN 51411-04-2 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo- (9CI) (CA INDEX NAME)



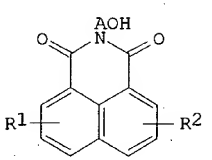
RN 51411-04-2 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo- (9CI) (CA INDEX NAME)



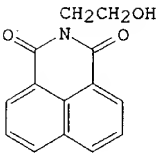
L17 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1977:145941 CAPLUS
DN 86:145941
TI Use of 2-(hydroxyalkyl)-1H-benz[de]isoquinoline-1,3(2H)-diones as antiallergy agents
IN Wade, Peter C.
PA Squibb, E. R., and Sons, Inc., USA
SO U.S., 5 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4006238	A	19770201	US 1975-608433	19750828

GI



I



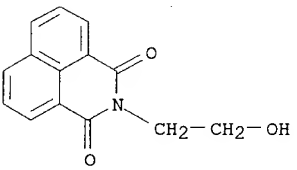
II

AB **Pharmaceutical** compns. contg. 2-(hydroxyalkyl)-1H-benz[de]isoquinoline-1,3(2H)-diones I, (R1 and R2 = H, Cl, Br, F, Me, or OMe and are at the 7- or 8-position or the 5- or 6-position, resp.; A = straight or branched chain C1-6 alkylene are prepd. and are useful for treating allergies. For example, by refluxing naphthalic anhydride [81-84-5] and ethanolamine [141-43-5] for 3 h in H2O, 2-(2-dione (II) [**5450-40-8**] was obtained. When administered i.p. to rats in 2 doses of 75 mg/kg each, II inhibited passive cutaneous anaphylaxis by 50%.

IT **5450-40-8P 6914-97-2P 55396-21-9P**
RL: PREP (Preparation)
(prepn. of, as antiallergy agent)

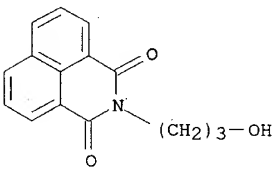
RN 5450-40-8 CAPLUS

CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)



RN 6914-97-2 CAPLUS

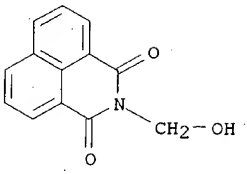
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(3-hydroxypropyl)- (9CI) (CA INDEX NAME)



RN 55396-21-9 CAPLUS

CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(hydroxymethyl)- (9CI) (CA INDEX NAME)

09758917



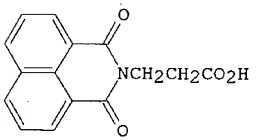
09758917

=> d 1-2 fbib abs hitstr

L20 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 1987:131724 CAPLUS
DN 106:131724
TI N-(2-Carboxy)-ethyl-1,8-naphthalene imide and its salts for the treatment of diabetic retinopathies and neuropathies
IN Malizia, Paolo
PA International Pharmaceutical Associated S.r.l. (IPA), Italy
SO Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DT **Patent**
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 206322	A2	19861230	EP 1986-108615	19860624
	EP 206322	A3	19900307		
	EP 206322	B1	19920826		
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
				IT 1985-21322	19850627
	AT 79755	E	19920915	AT 1986-108615	19860624
				IT 1985-21322	19850627
				EP 1986-108615	19860624

GI



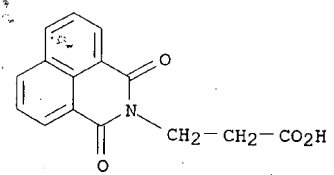
I

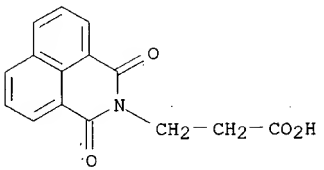
AB The title compd. (IPA 955) (I) and its lysine and N-methylglucamine salts inhibit aldose reductase and are therefore useful for treatment of retinopathy, **neuropathy**, and nephropathy which result from accumulation of polyols in the effected tissues in diabetes. I also inhibited blood platelet aggregation in vitro at 1.25 mM approx. as effectively as ticlopidine. I was prepd. by refluxing naphthalene-1,8-dicarboxylic acid with .beta.-alanine in aq. NaOH.

IT **86703-96-0P 107392-40-5P 107439-30-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, for nephropathy, **neuropathy**, and retinopathy treatment in diabetes mellitus)

RN 86703-96-0 CAPLUS

CN 1H-Benz[de]isoquinoline-2(3H)-propanoic acid, 1,3-dioxo- (9CI) (CA INDEX NAME)

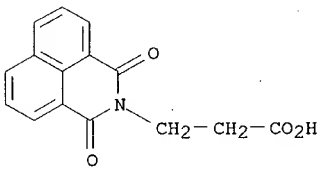




RN 107392-40-5 CAPLUS
CN L-Lysine, mono(1,3-dioxo-1H-benz[de]isoquinoline-2(3H)-propanoate) (9CI) (CA INDEX NAME)

CM 1

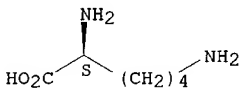
CRN 86703-96-0
CMF C15 H11 N O4



CM 2

CRN 56-87-1
CMF C6 H14 N2 O2
CDES 5:L

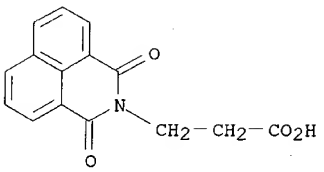
Absolute stereochemistry.



RN 107439-30-5 CAPLUS
CN D-Glucitol, 1-deoxy-1-(methylamino)-, 1,3-dioxo-1H-benz[de]isoquinoline-2(3H)-propanoate (salt) (9CI) (CA INDEX NAME)

CM 1

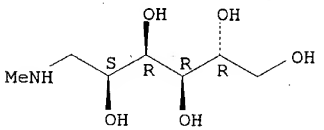
CRN 86703-96-0
CMF C15 H11 N O4



CM 2

CRN 6284-40-8
CMF C7 H17 N O5
CDES *

Absolute stereochemistry.



L20 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
AN 1974:576158 CAPLUS
DN 81:176158
TI Compositions for diabetic complications
IN Sestanj, Kazimir; Simard-Duquesne, Nicole; Dvornik, Dusan M.
PA Ayerst McKenna and Harrison Ltd.
SO U.S., 7 pp.
CODEN: USXXAM
DT **Patent**
LA English
FAN.CNT 1

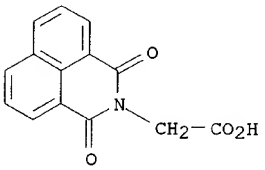
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 3821383	A	19740628	US 1972-270357	19720710

GI For diagram(s), see printed CA Issue.

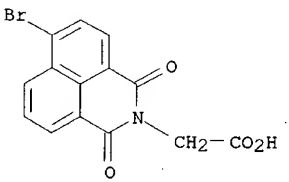
AB Diabetes mellitus assocd. complications such as cataracts, **neuropathy**, nephropathy, and retinopathy in a diabetic mammal are prevented by administration of a compn. contg. I (X = 5-O2N, 5-H2N, or 6-Br). Thus, 1,8-naphthalic acid anhydride, glycine, and DMF are heated and stirred at reflux for 2 hr to give 1,3-dioxo-1H-benz[de]isoquinoline-2(3H)-acetic acid (I, X = H) 271-2.degree.. Similarly prepd. were (X and m.p. given): 6-Br, 279-81.degree.; 5-O5N, 273-5.degree.. Treatment of galactosemic or diabetic rats with the above compds. showed that the lenses of the treated rats contained significantly less (.apprx.35%) dulcitol than those of untreated rats. The compds. lessen the formation of irreversible opacities and cataracts in the lens galactosemic rats and show a protective effect against the ac dulcitol in the sciatic nerves of the galactosemic rats; this analogous to the accumulation of sorbitol in advanced **neuropat** . The compds. also decreased sorbitol accumulation in the len sciatic nerves and reduced the no. of lenses with opacities no expected to occur in diabetic rats.

IT **51411-04-2 53497-33-9 53497-34-0**
RL: BIOL (Biological study)
(diabetic complications treatment with)

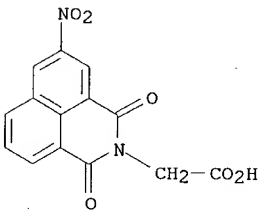
RN 51411-04-2 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo- (9CI) (CA INDEX NAME)



RN 53497-33-9 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 6-bromo-1,3-dioxo- (9CI) (CA INDEX NAME)



RN 53497-34-0 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 5-nitro-1,3-dioxo- (9CI) (CA INDEX NAME)



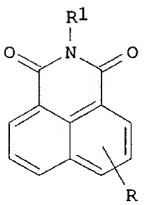
L23 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
AN 2000:824227 CAPLUS
DN 133:362713
TI Preparation of 2-carboxyalkyl-2,3-dihydro-1H-benz[d,e]isoquinoline-1,3-diones as p75 **nerve** growth factor receptor antagonists
IN Ross, Gregory M.; Shamovsky, Igor L.; Marone, Sandra; Weaver, Donald F.; Riopelle, Richard J.
PA Queen's University At Kingston, Can.
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000069828	A1	20001123	WO 2000-CA541	20000511

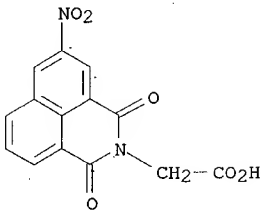
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 1999-310883 A 19990517
US 1999-457606 A 19991208

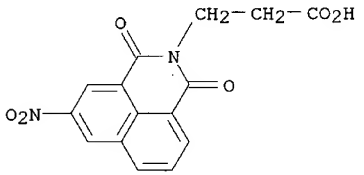
OS MARPAT 133:362713
GI



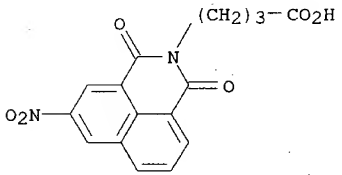
AB Title compds.[I; R = 5- or 6-nitro; R1 = carboxyalkyl] were prepd. Thus, 3-nitro-1,8-naphthalic anhydride was cyclocondensed with glycine to give I (R = 5-NO2, R1 = CH2CO2H). Data for biol. activity of I were given.
IT **53497-34-0P 307299-09-8P 307299-10-1P 307299-13-4P 307299-14-5P 307299-15-6P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-carboxyalkyl-2,3-dihydro-1H-benz[d,e]isoquinoline-1,3-diones as p75 **nerve** growth factor receptor antagonists)
RN 53497-34-0 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 5-nitro-1,3-dioxo- (9CI) (CA INDEX NAME)



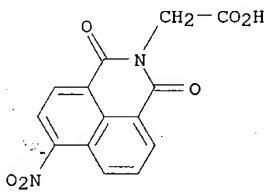
RN 307299-09-8 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-propanoic acid, 5-nitro-1,3-dioxo- (9CI) (CA INDEX NAME)



RN 307299-10-1 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-butanoic acid, 5-nitro-1,3-dioxo- (9CI) (CA INDEX NAME)

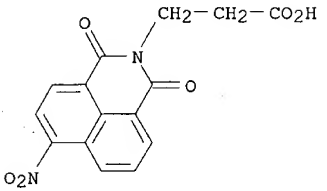


RN 307299-13-4 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 6-nitro-1,3-dioxo- (9CI) (CA INDEX NAME)

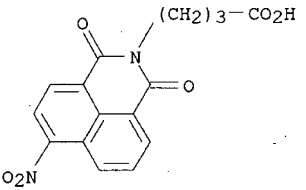


RN 307299-14-5 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-propanoic acid, 6-nitro-1,3-dioxo- (9CI)

(CA INDEX NAME)



RN 307299-15-6 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-butanoic acid, 6-nitro-1,3-dioxo- (9CI) (CA INDEX NAME)



RE.CNT 6
RE
(1) Allelix Biopharma; WO 9817278 A 1998 CAPLUS
(2) Du Pont Pharm Co; WO 0000472 A 2000 CAPLUS
(3) I P A International Pharmaceut; EP 0206322 A 1986 CAPLUS
(4) Ki I Endokrinologii; FR 2521139 A 1983 CAPLUS
(5) Knoll Ag; EP 0268093 A 1988 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

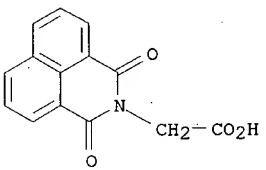
L23 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
AN 1985:405384 CAPLUS
DN 103:5384
TI Effects of a fructose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy in streptozotocin-treated rats
AU Hotta, Nigishi; Kakuta, H.; Fukasawa, H.; Kimura, M.; Koh, N.; Iida, M.; Terashima, H.; Morimura, T.; Sakamoto, N.
CS Sch. Med., Nagoya Univ., Nagoya, 466, Japan
SO Diabetologia (1985), 28(3), 176-80
CODEN: DBTGAJ; ISSN: 0012-186X
DT Journal
LA English
AB Streptozotocin-diabetic rats were maintained on a 72% fructose [57-48-7] diet for 4 wk and some were treated with an aldose reductase [9028-31-3] inhibitor (either alrestatin [**51411-04-2**] 0.9 or ONO-2235 [82159-09-9] 50 mg/kg/day). Fructose feeding significantly influenced the development of impaired motor **nerve** conduction velocity in the diabetic rats and this effect was pos. correlated with sorbitol accumulation in the sciatic **nerve** of diabetic rats maintained on a fructose-rich diet. Treatment with ONO-2235, a new aldose reductase

inhibitor, prevented both slowing of motor **nerve** conduction velocity and elevation of **nerve** sorbitol concn. On the other hand, erythrocyte sorbitol [50-70-4] levels were significantly correlated to those of the sciatic **nerve** and the retina in these animals. Thus, an increased polyol pathway activity may be related to the pathogenesis of diabetic neuropathy and erythrocyte sorbitol concns. may prove a useful indicator for the presence of diabetic complications.

IT **51411-04-2**
RL: BIOL (Biological study)
(aldose reductase inhibition by, neuropathy and diabetes in response to fructose-high diet decrease by)

RN 51411-04-2 CAPLUS

CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo- (9CI) (CA INDEX NAME)



L23 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

AN 1979:179853 CAPLUS

DN 90:179853

TI Aldose reductase inhibition: studies with alrestatin

AU Gabbay, Kenneth H.; Spack, Norman; Loo, Sherry; Hirsch, Harry J.; Ackil, Albert A.

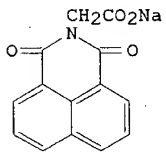
CS Dep. Med., Child. Hosp. Med. Cent., Boston, Mass., USA

SO Metab., Clin. Exp. (1979), 28(4, Suppl. 1), 471-88
CODEN: METAAJ; ISSN: 0026-0495

DT Journal

LA English

GI



I

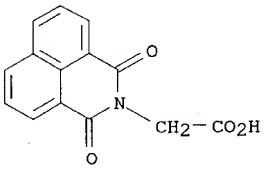
AB In normal subjects and in selected diabetic patients with severe peripheral neuropathy, alrestatin Na (I) [**51876-97-2**] given either i.v. (50 mg/kg) or orally (4 g/day) produced no acute toxicity. The serum half-life of I was about 1 h, and 99% was recovered in the urine within 24 h. Two diabetic patients receiving I i.v. reported subjective improvements in clin. symptoms 2 days after the start of infusions. These improvements lasted about 3 wk after therapy was discontinued. However,

there were no objective changes in peripheral **nerve** condition velocities or on neurologic examn. In a 30-day oral trial with I in diabetics, there were no subjective improvements in clin. symptoms nor were there objective improvements on neurol. examn. or in peripheral **nerve** conduction velocities. In this study, peak serum levels of I were about 3 times lower than those obtained on i.v. administration, and apparently a high peak serum level is crit. to the attainment of adequate tissue drug concns. Further, the patients were suffering from severe clin. peripheral neuropathy, which could represent a stage of permanent irreversible **nerve** damage.

IT **51876-97-2**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, in diabetes and neuropathy)

RN 51876-97-2 CAPLUS

CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo-, sodium salt (9CI) (CA INDEX NAME)



● Na

L23 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS

AN 1974:475855 CAPLUS

DN 81:75855

TI Polyol accumulation in galactosemic and diabetic rats. Control by an aldose reductase inhibitor

AU Dvornik, D.; Simare-Duquesne, N.; Krami, M.; Sestanj, K.; Gabbay, K. H.; Kinoshita, J. H.; Varma, S. D.; Merola, L. O.

CS Dep. Biochem., Ayerst Res. Lab., Montreal, Que., Can.

SO Science (1973), 182(4117), 1146-8
CODEN: SCIEAS

DT Journal

LA English

GI For diagram(s), see printed CA Issue.

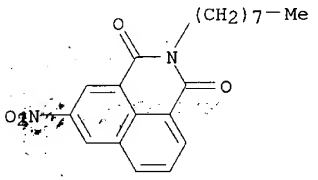
AB An orally active inhibitor of aldose reductase, 1,3-dioxo-1H-benz[de]-isoquinoline-2(3H)acetic acid, (AY-22, 284)(I), prevented cataractous changes in cultured lenses exposed to high concns. of galactose. When given orally, I markedly decreased the accumulation of polyols in the lenses and sciatic nerves of galactosemic rats with rats with streptozotocin-induced diabetes. In addn., treatment of galactosemic rats with I effectively suppressed the formation of cataracts.

IT **51411-04-2**
RL: BIOL (Biological study)
(cataract and polyols in eye lens and sciatic **nerve** in response to, in diabetes and galactosemia)

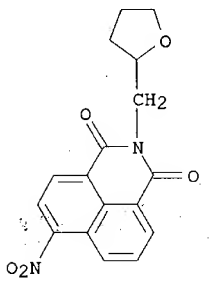
RN 51411-04-2 CAPLUS

CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo- (9CI) (CA INDEX NAME)

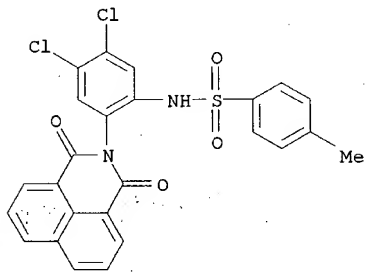
RN 207107-67-3 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 5-nitro-2-octyl- (9CI) (CA INDEX NAME)



RN 207107-68-4 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-nitro-2-[(tetrahydro-2-furanyl)methyl]- (9CI) (CA INDEX NAME)

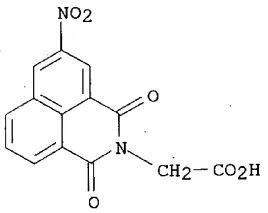


RN 207107-69-5 CAPLUS
CN Benzenesulfonamide, N-[4,5-dichloro-2-(1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)phenyl]-4-methyl- (9CI) (CA INDEX NAME)

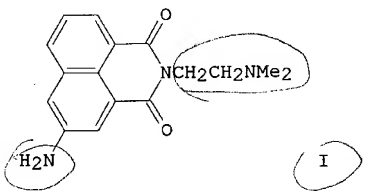


RN 207107-70-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-nitro-2-(3-pyridinylmethyl)- (9CI) (CA INDEX NAME)

IT **53497-34-0P**
RL: PREP (Preparation)
(prepn. of, as fluorescent marker for hypoxic **tumor** cells)
RN 53497-34-0 CAPLUS
CN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 5-nitro-1,3-dioxo- (9CI) (CA INDEX NAME)



L29 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1985:89672 CAPLUS
DN 102:89672
TI Computer assisted structure-activity correlations. Evaluation of benzo(de)isoquinoline-1,3-diones and related compounds as **antitumor** agents
AU Paull, K. D.; Nasr, M.; Narayanan, V. L.
CS Div. Cancer Treat., Natl. Cancer Inst., Bethesda, MD, 20205, USA
SO Arzneim.-Forsch. (1984), 34(10), 1243-6
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA English
GI

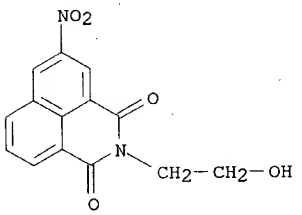


AB Computer assisted evaluations of benzo(de)isoquinoline-1,3-diones and related compds. screened for **antitumor** activity against P388 lymphocytic leukemia and L1210 lymphoid leukemia are presented. Two important features necessary for good anticancer activity are the nature of the imide side-chain and the type of substituent on the arom. portion. Based on these considerations NSC 308847 [1H-benzo(de)isoquinoline-1,3(2H)dione,5-amino-2-(2-dimethylaminoethyl)](I) [69408-81-7] has been selected for preclin. toxicol. studies.

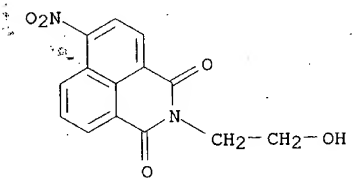
IT **6914-62-1**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antitumor** activity of, computer assisted structure-activity correlations in)

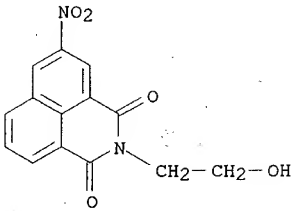
09758917

DN 115:67772
TI Fluorescent markers for hypoxic cells: a study of novel heterocyclic compounds that undergo bioreductive binding
AU Hodgkiss, R. J.; Begg, A. C.; Middleton, R. W.; Parrick, J.; Stratford, M. R. L.; Wardman, P.; Wilson, G. D.
CS Gray Lab. Cancer Res., Mt. Vernon Hosp., Northwood/Middlesex, HA6 2JR, UK
SO Biochem. Pharmacol. (1991), 41(4), 533-41
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB The bioreductive metab. and binding of nitroarom. compds. has been suggested as a method for the identification of hypoxic **tumor** cells. Bound metabolites of suitable nitroaryl compds. (and some other reducible arom. compds.) may fluoresce, offering an alternative to radiolabeling or NMR, etc., as a diagnostic method. In this study the synthesis of some heteroarom. nitro compds. is given together with the results obtained from testing of these and other mainly nitro arom. compds. in vitro as potential bioreductive fluorescent probes for hypoxic cells in tumors. Compds. were incubated with oxygenated or hypoxic mammalian cell suspensions for various times before evaluation of the cellular fluorescence from bioreductive metabolites by fluorescence microscopy and flow cytometry. Among those compds. yielding fluorescent metabolites in cells, considerable variation in hypoxic-to-oxic differential fluorescence was obsd. The in vitro mammalian cell test system showed several of the compds. to be sufficiently promising to merit further investigation in vivo.
IT **79070-65-8 92060-89-4**
RL: ANST (Analytical study)
(fluorescent marker, for hypoxic **tumor** cells)
RN 79070-65-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-5-nitro- (9CI) (CA INDEX NAME)

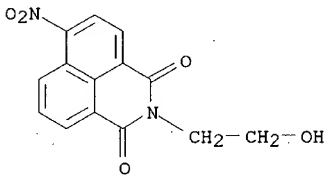


RN 92060-89-4 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-6-nitro- (9CI) (CA INDEX NAME)

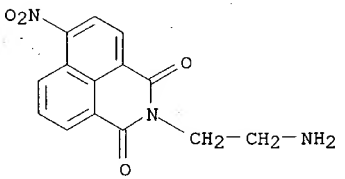




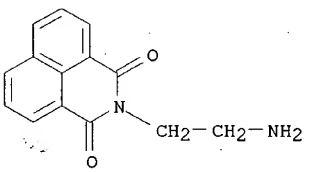
RN 92060-89-4 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-6-nitro- (9CI) (CA INDEX NAME)



RN 162265-48-7 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminoethyl)-6-nitro- (9CI) (CA INDEX NAME)



RN 162265-51-2 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminoethyl)- (9CI) (CA INDEX NAME)



L29 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS
AN 1991:467772 CAPLUS

analogs

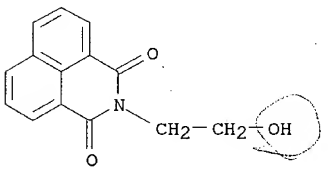
AU Miller, Kelli E.; Grace, James M.; Macdonald, Timothy L.
CS Dep. Chem., Univ. Virginia, Charlottesville, VA, 22901, USA

SO Bioorg. Med. Chem. Lett. (1994), 4(13), 1643-5
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English

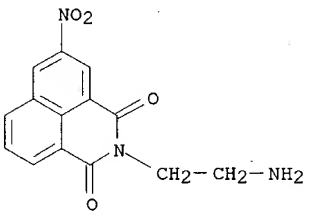
AB Amonafide (4-aminobenzoisoquinolinedione) and its structural analog, mitonafide, have been shown to stabilize topoisomerase II cleavable complexes. The position of the nitro group and structural modifications of the side chain influence the interactions between drug, enzyme, and DNA. It was shown that the analogs with the nitro in the 5-position are the most potent inhibitors in this structural class.

IT **5450-40-8P 79070-63-6P 79070-65-8P**
92060-89-4P 162265-48-7P 162265-51-2P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mitonafide analog, as **antitumor** agent; stabilization of DNA topoisomerase II-DNA cleavable complex by mitonafide analogs)

RN 5450-40-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)



RN 79070-63-6 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminoethyl)-5-nitro- (9CI) (CA INDEX NAME)



RN 79070-65-8 CAPLUS
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-5-nitro- (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
AN 1998:268358 CAPLUS
DN 128:317269
TI Benzoisoquinolinedione neurotrophin antagonist compositions and therapeutic use
IN Tehim, Ashok; **Chen, Xiannong**
PA Allelix Biopharmaceuticals Inc., Can.; Tehim, Ashok; Chen, Xiannong
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9817278	A1	19980430	WO 1997-CA779	19971020
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	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
				GB 1996-21902	A 19961021
				GB 1997-10904	A 19970527
	AU 9746968	A1	19980515	AU 1997-46968	19971020
	AU 728523	B2	20010111		
				GB 1996-21902	A 19961021
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				WO 1997-CA779	W 19971020
	EP 930883	A1	19990728	EP 1997-909098	19971020
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				GB 1996-21902	A 19961021
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				WO 1997-CA779	W 19971020
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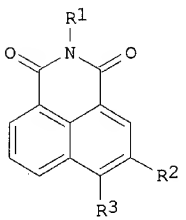
				GB 1997-10904	A 19970527
				WO 1997-CA779	W 19971020

OS MARPAT 128:317269
GI

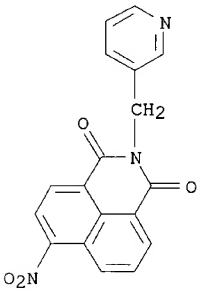


I

AB Pharmaceutical compns. comprising I (R1 = alkyl, aryl-lower alkyl, heterocyclyl-lower alkyl, etc.; R2, R3 = H, NO2, halo, di(lower alkyl)amino, cyano, etc.), or pharmaceutically acceptable salts or certain in vivo hydrolyzable esters or amides thereof, in an amt. effective to inhibit neurotrophin-mediated activity, and a suitable carrier, are described. The compns. are useful for inhibiting undesirable neurotrophin-mediated activity, e.g. the neurite outgrowth that occurs in some neurodegenerative disease states. N-[5-nitro-1H-benz[de]isoquinoline-1,3(2H)-dione]-2-aminoethanol (II) was prepd. from 3-nitro-1,8-naphthalic anhydride and 2-hydroxyethylhydrazine. II was tested for ability to inhibit neurite outgrowth, as well as in an animal model of neuropathic pain. Compds. of the invention were also tested for ability to inhibit NGF binding to P75 and TrkA.

09758917

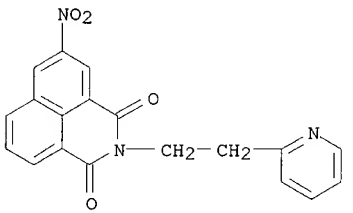
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-nitro-2-(3-pyridinylmethyl)-(9CI)
MF C18 H11 N3 O4



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):37

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 5-nitro-2-[2-(2-pyridinyl)ethyl]-(9CI)
MF C19 H13 N3 O4



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

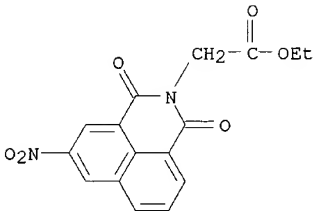
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN Nerve growth factor (9CI)
MF Unspecified
CI PMS, COM, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 5-nitro-1,3-dioxo-, ethyl ester (9CI)

09758917

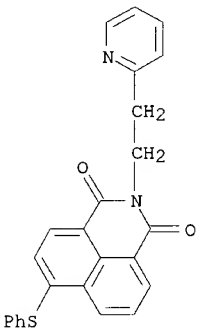
MF C16 H12 N2 O6



(21)

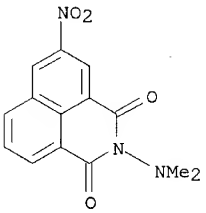
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-(phenylthio)-2-[2-(2-pyridinyl)ethyl]- (9CI)
MF C25 H18 N2 O2 S



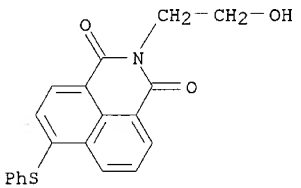
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(dimethylamino)-5-nitro- (9CI)
MF C14 H11 N3 O4



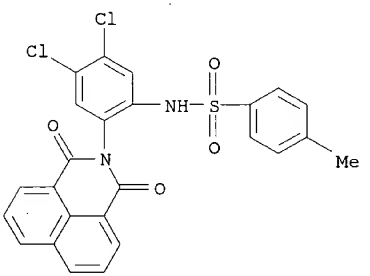
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-6-(phenylthio)-(9CI)
MF C20 H15 N O3 S



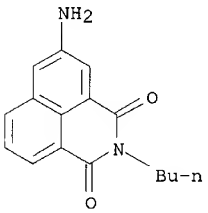
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN Benzenesulfonamide, N-[4,5-dichloro-2-(1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)phenyl]-4-methyl- (9CI)
MF C25 H16 Cl2 N2 O4 S



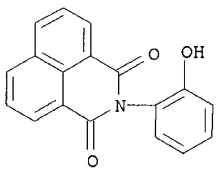
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 5-amino-2-butyl- (9CI)
MF C16 H16 N2 O2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyphenyl)- (9CI)
MF C18 H11 N O3

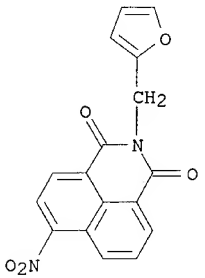


10

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

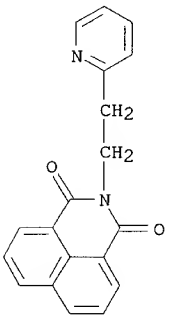
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-furanylmethyl)-6-nitro- (9CI)
MF C17 H10 N2 O5

09758917



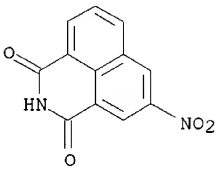
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-[2-(2-pyridinyl)ethyl]- (9CI)
MF C19 H14 N2 O2



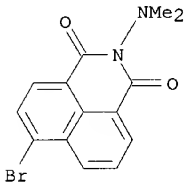
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 5-nitro- (9CI)
MF C12 H6 N2 O4



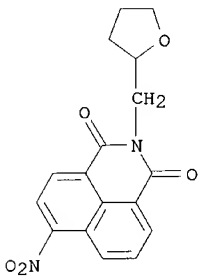
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-bromo-2-(dimethylamino)- (9CI)
MF C14 H11 Br N2 O2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-nitro-2-[(tetrahydro-2-furanyl)methyl]- (9CI)
MF C17 H14 N2 O5

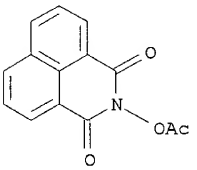


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS

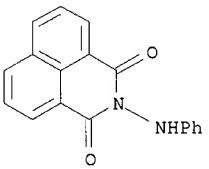
09758917

IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(acetyloxy)- (9CI)
MF C14 H9 N O4



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

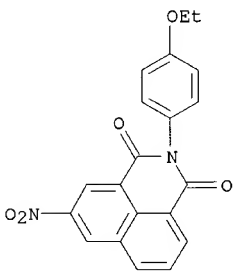
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(phenylamino)- (9CI)
MF C18 H12 N2 O2



91

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

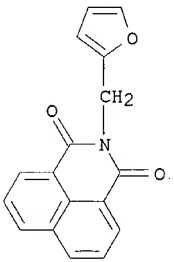
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(4-ethoxyphenyl)-5-nitro- (9CI)
MF C20 H14 N2 O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

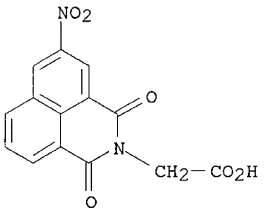
09758917

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-furanylmethyl)- (9CI)
MF C17 H11 N O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

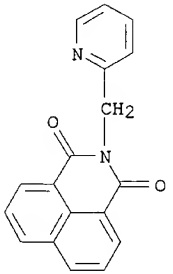
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 5-nitro-1,3-dioxo- (9CI)
MF C14 H8 N2 O6



21

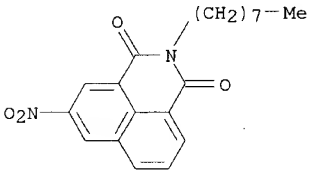
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-pyridinylmethyl)- (9CI)
MF C18 H12 N2 O2



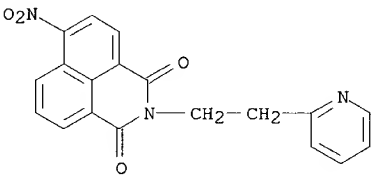
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 5-nitro-2-octyl- (9CI)
MF C20 H22 N2 O4



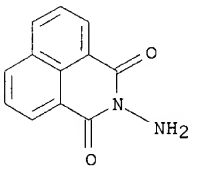
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6-nitro-2-[2-(2-pyridinyl)ethyl]-
(9CI)
MF C19 H13 N3 O4



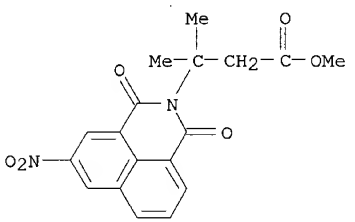
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-amino- (9CI)
MF C12 H8 N2 O2



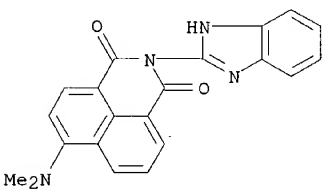
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

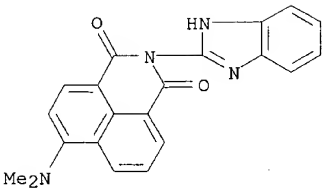
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-2(3H)-propanoic acid, .beta.,.beta.-dimethyl-5-nitro-1,3-dioxo-, methyl ester (9CI)
MF C18 H16 N2 O6



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

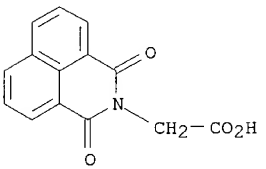
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(1H-benzimidazol-2-yl)-6-(dimethylamino)- (9CI)
MF C21 H16 N4 O2





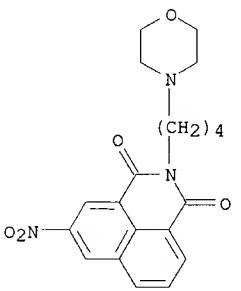
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-2(3H)-acetic acid, 1,3-dioxo- (9CI)
MF C14 H9 N O4
CI COM



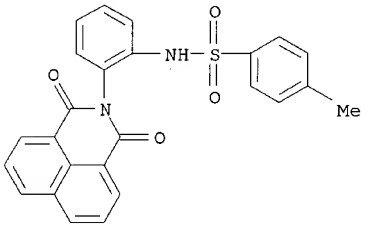
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-[4-(4-morpholinyl)butyl]-5-nitro- (9CI)
MF C20 H21 N3 O5



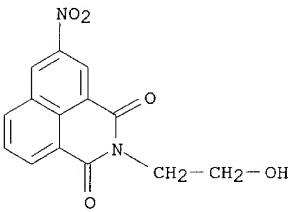
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN Benzenesulfonamide, N-[2-(1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)phenyl]-4-methyl- (9CI)
MF C25 H18 N2 O4 S



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

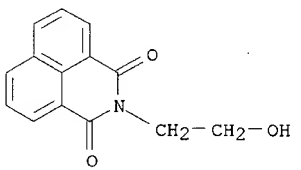
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)-5-nitro- (9CI)
MF C14 H10 N2 O5



(3)

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

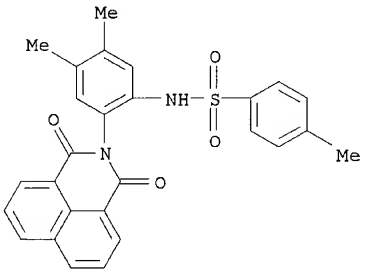
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyethyl)- (9CI)
MF C14 H11 N O3



(4)

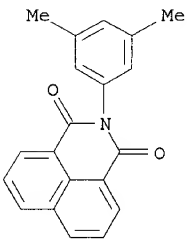
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN Benzenesulfonamide, N-[2-(1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl)-4,5-dimethylphenyl]-4-methyl- (9CI)
MF C27 H22 N2 O4 S



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

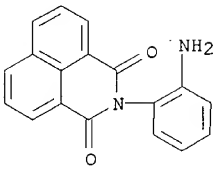
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(3,5-dimethylphenyl)- (9CI)
MF C20 H15 N O2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

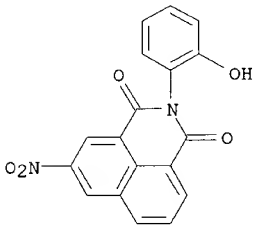
L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-aminophenyl)- (9CI)
MF C18 H12 N2 O2

71



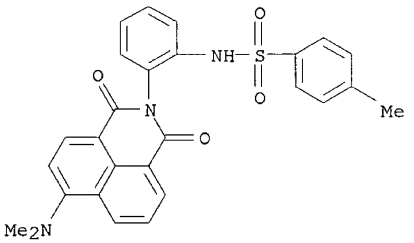
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyphenyl)-5-nitro- (9CI)
MF C18 H10 N2 O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN Benzenesulfonamide, N-[2-[6-(dimethylamino)-1,3-dioxo-1H-benz[de]isoquinolin-2(3H)-yl]phenyl]-4-methyl- (9CI)
MF C27 H23 N3 O4 S



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS

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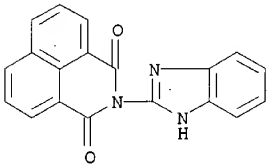
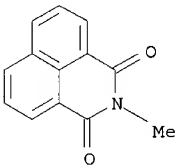
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(1H-benzimidazol-2-yl)- (9CI)
MF C19 H11 N3 O2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L6 38 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-methyl- (9CI)
MF C13 H9 N O2



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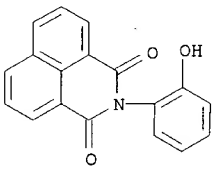
=> s e3
L1 1 6917-30-2/RN

=> d all

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **6917-30-2** REGISTRY
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-(2-hydroxyphenyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Naphthalimide, N-(o-hydroxyphenyl)- (7CI, 8CI)
FS 3D CONCORD
MF C18 H11 N O3
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CHEMCATS, IFICDB, IFIPAT, IFIUDB, TOXLIT
(*File contains numerically searchable property data)

Ring System Data

Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count
C6	C6	6	C6	46.150.18	1
C5N-C6-C6	NC5-C6-C6	6-6-6	C12N	1784.14.8	1



Calculated Properties (CALC)

CODE	PROPERTY	VALUE	CONDITION	NOTE
HD	H donors	1		ACD (1)
HAC	H acceptors	4		ACD (1)
MW	Molecular Weight	289.28		ACD (1)
LOGP	logP	1.991+/-0.611		ACD (1)
LOGD	logD	1.99	pH 1	ACD (1)
LOGD	logD	1.99	pH 4	ACD (1)
LOGD	logD	1.99	pH 7	ACD (1)
LOGD	logD	1.97	pH 8	ACD (1)
LOGD	logD	1.23	pH 10	ACD (1)
PKA	pKa	9.32+/-0.20	Most Acidic	ACD (1)
SLB.MOL	Molar Solubility	<0.01 mol/L	pH 1	ACD (1)
SLB.MOL	Molar Solubility	<0.01 mol/L	pH 4	ACD (1)
SLB.MOL	Molar Solubility	<0.01 mol/L	pH 7	ACD (1)
SLB.MOL	Molar Solubility	<0.01 mol/L	pH 8	ACD (1)
SLB.MOL	Molar Solubility	<0.01 mol/L	pH 10	ACD (1)

09758917

(1) Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 ((C) 1994-2002 ACD)

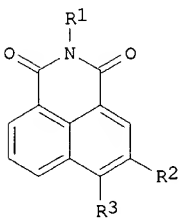
2 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1

AN 128:317269 CA
TI Benzoisoquinolinedione neurotrophin antagonist compositions and therapeutic use
IN Tehim, Ashok; Chen, Xiannong
PA Allelix Biopharmaceuticals Inc., Can.; Tehim, Ashok; Chen, Xiannong
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-47
ICS C07D221-14; C07D401-04; C07D401-06
CC 1-11 (Pharmacology)
Section cross-reference(s): 27, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9817278	A1	19980430	WO 1997-CA779	19971020
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9746968	A1	19980515	AU 1997-46968	19971020
	AU 728523	B2	20010111		
	EP 930883	A1	19990728	EP 1997-909098	19971020
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001503397	T2	20010313	JP 1998-518756	19971020
	BR 9712424	A	20011120	BR 1997-12424	19971020
PRAI	GB 1996-21902	19961021			
	GB 1997-10904	19970527			
	WO 1997-CA779	19971020			

GI



I

AB Pharmaceutical compns. comprising I (R1 = alkyl, aryl-lower alkyl, heterocyclyl-lower alkyl, etc.; R2, R3 = H, NO2, halo, di(lower alkyl)amino, cyano, etc.), or pharmaceutically acceptable salts or certain in vivo hydrolyzable esters or amides thereof, in an amt. effective to inhibit neurotrophin-mediated activity, and a suitable carrier, are described. The compns. are useful for inhibiting undesirable neurotrophin-mediated activity, e.g. the neurite outgrowth that occurs in some neurodegenerative disease states. N-[5-nitro-1H-benz[de]isoquinoline-1,3(2H)-dione]-2-aminoethanol (II) was prepd. from 3-nitro-1,8-naphthalic anhydride and 2-hydroxyethylhydrazine. II was tested for ability to inhibit neurite outgrowth, as well as in an animal model of neuropathic pain. Compds. of the invention were also tested for ability to inhibit NGF binding to P75 and TrkA.

ST benzoisoquinolinedione neurotrophin antagonist neurite outgrowth inhibition; neurodegenerative disease benzoisoquinolinedione neurotrophin antagonist prepn; neuropathic pain benzoisoquinolinedione neurotrophin antagonist

IT Pain
Skin diseases
(allodynia, tactile; benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT Analgesics
Drug delivery systems
Neurons
(benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT Brain-derived neurotrophic factor
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT Neurotrophic factors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT TrkA (receptor)
p75NGFR (receptor)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT Neurite outgrowth
(inhibition; benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT Pain
(neuropathic; benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT Hyperalgesia
(thermal; benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT 9061-61-4, NGF
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT 79070-65-8P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

IT 2382-08-3 5450-40-8 5690-46-0 5690-46-0D, esters and amides 5810-79-7 6917-30-2D, esters and amides 15965-03-4 15965-03-4D, esters and amides 51411-04-2D, esters and amides 53497-34-0 53497-34-0D, esters and amides 66266-36-2 69408-78-2 74240-33-8 79070-65-8D, esters and amides 94887-57-7 100873-54-9 130001-49-9 162265-47-6 194610-48-5 206982-84-5 207107-62-8 207107-63-9 207107-64-0 207107-65-1 207107-66-2 207107-67-3 207107-68-4 207107-69-5 207107-70-8 207107-71-9 207107-72-0 207107-73-1 207107-74-2 207107-75-3 207107-76-4 207107-77-5 207107-78-6 207107-79-7 207107-80-0
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzoisoquinolinedione neurotrophin antagonist compns. and therapeutic use)

REFERENCE 2

AN 67:91380 CA
TI 1,8-Naphthalimide ultraviolet stabilizers for polymers
IN Dressler, Hans; Reabe, Kenneth G.
PA Koppers Co., Inc.
SO U.S., 3 pp.
CODEN: USXXAM
DT Patent
LA English
NCL 260045800
CC 36 (Plastics Manufacture and Processing)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3340225		19670905	US	19640617

GI For diagram(s), see printed CA Issue.
AB Polymers are stabilized against uv light degradation by the title compds. (I), where R is H or OH, and R1 is OEt or H when I was added at 0.1-4 wt.%. Thus, 40 g. 1,8-naphthalic anhydride, 22 g. o-aminophenol, 100 ml. BuOH, and 100 ml. PhMe were refluxed for 6 hrs. while 3.1 ml. H2O was removed. The residue was slurried in PhMe and filtered to yield 47.2 g. product, which, when recrystd. from PhNO2, yielded 8.7 g. I (R1 = H, R = OH), m. 325-330.degree.. This I (0.1 part) was blended with 100 parts polystyrene in a jar mill and the stabilized beads were extruded into pellets and formed into 2-in.-diam. disks by injection molding. The molded disks were exposed to uv radiation under a 325-w. lamp for 120 hrs. The yellowness index before exposure was 9.8 and after exposure was 13.5, giving a yellowness factor of 3.7. A control without stabilizer had a yellowness index of 8.4 before exposure and 15.3 after exposure, giving a yellowness factor of 6.9. I (R = H, R1 = OEt) was also used and low-d. polyethylene was also stabilized.
ST NAPHTHALAMIDES UV STABILIZERS; UV STABILIZERS NAPHTHALAMIDES; POLYSTYRENE UV STABILIZING; POLYETHYLENE UV STABILIZING; PLASTICS UV STABILIZING
IT Light, ultraviolet, chemical and physical effects
(stabilizers, naphthalimide derivs. as, for ethylene polymers or styrene polymers)
IT 6917-30-2 15042-12-3
RL: USES (Uses)
(as ultraviolet light stabilizer for ethylene polymers or styrene polymers)
IT 9002-88-4, uses and miscellaneous 9003-53-6, uses and miscellaneous
RL: USES (Uses)

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(ultraviolet light stabilizers for, naphthalimide derivs. as)

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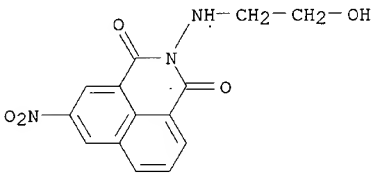
=> s el
L1 1 "ALE 0540"/CN

=> d scan

L1 1 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-[(2-hydroxyethyl)amino]-5-nitro-
(9CI)
MF C14 H11 N3 O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

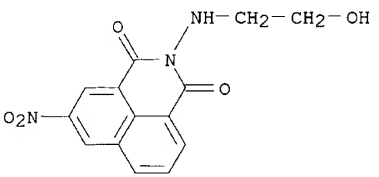
ALL ANSWERS HAVE BEEN SCANNED

=> d all

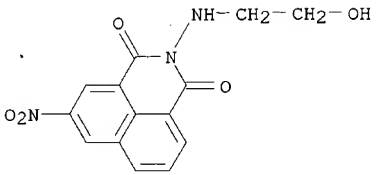
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 234779-34-1 REGISTRY
CN 1H-Benz[de]isoquinoline-1,3(2H)-dione, 2-[(2-hydroxyethyl)amino]-5-nitro-
(9CI) (CA INDEX NAME)
OTHER NAMES:
CN **ALE 0540**
FS 3D CONCORD
MF C14 H11 N3 O5
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, TOXLIT

Ring System Data

Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count
C5N-C6-C6	NC5-C6-C6	6-6-6	C12N	1784.14.8	1



09758917



Calculated Properties (CALC)

CODE	PROPERTY	VALUE	CONDITION	NOTE
HD	H donors	2		ACD (1)
HAC	H acceptors	8		ACD (1)
MW	Molecular Weight	301.25		ACD (1)
LOGP	logP	0.290+/-0.626		ACD (1)
LOGD	logD	0.29	pH 1	ACD (1)
LOGD	logD	0.29	pH 4	ACD (1)
LOGD	logD	0.29	pH 7	ACD (1)
LOGD	logD	0.29	pH 8	ACD (1)
LOGD	logD	0.29	pH 10	ACD (1)
SLB.MOL	Molar Solubility	>=0.01 - <0.1 mol/L	pH 1	ACD (1)
SLB.MOL	Molar Solubility	>=0.01 - <0.1 mol/L	pH 4	ACD (1)
SLB.MOL	Molar Solubility	>=0.01 - <0.1 mol/L	pH 7	ACD (1)
SLB.MOL	Molar Solubility	>=0.01 - <0.1 mol/L	pH 8	ACD (1)
SLB.MOL	Molar Solubility	>=0.01 - <0.1 mol/L	pH 10	ACD (1)

(1) Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 ((C) 1994-2002 ACD)

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1

AN 135:298810 CA
TI Use of NGF antagonists for the prevention or treatment of chronic visceral pain
IN Diop, Laurent; Delafoy, Laure
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
ICS A61K031-473; A61K039-395; A61P015-00; A61P001-06; A61P001-18; A61P001-14; A61P001-00
CC 1-11 (Pharmacology)
Section cross-reference(s): 2, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001078698	A2	20011025	WO 2001-EP3490	20010326

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,

HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

FR 2807660 A1 20011019 FR 2000-4782 20000413

PRAI FR 2000-4782 20000413

AB A nerve growth factor (NGF) antagonist is used for the manuf. of a medicament intended for the prevention or treatment of chronic visceral pain. Corresponding pharmaceutical compns. are also disclosed.

ST NGF antagonist chronic visceral pain treatment

IT Analgesics
Drug delivery systems
Dysmenorrhea
Dyspepsia
(NGF antagonists for prevention or treatment of chronic visceral pain)

IT Nerve growth factor receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(NGF antagonists for prevention or treatment of chronic visceral pain)

IT Pain
(chronic; NGF antagonists for prevention or treatment of chronic visceral pain)

IT Digestive tract
(gastroesophageal reflux; NGF antagonists for prevention or treatment of chronic visceral pain)

IT Intestine, disease
(irritable bowel syndrome; NGF antagonists for prevention or treatment of chronic visceral pain)

IT Drug delivery systems
(oral; NGF antagonists for prevention or treatment of chronic visceral pain)

IT Viscera
(pain; NGF antagonists for prevention or treatment of chronic visceral pain)

IT Pancreas, disease
(pancreatitis; NGF antagonists for prevention or treatment of chronic visceral pain)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to NGF; NGF antagonists for prevention or treatment of chronic visceral pain)

IT Viscera
(visceralgia; NGF antagonists for prevention or treatment of chronic visceral pain)

IT 234779-34-1, ALE 0540
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NGF antagonists for prevention or treatment of chronic visceral pain)

IT 137010-36-7, NGF receptor tyrosine kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(NGF antagonists for prevention or treatment of chronic visceral pain)

IT 9061-61-4, Nerve growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NGF antagonists for prevention or treatment of chronic visceral pain)

REFERENCE 2

09758917

AN 131:125331 CA
TI Characterization of antiallodynic actions of ALE-0540, a novel nerve growth factor receptor antagonist, in the rat
AU Owolabi, Joshua B.; Rizkalla, Geihan; Tehim, Ashok; Ross, Gregory M.; Riopelle, Richard J.; Kamboj, Rajender; Ossipov, Michael; Bian, Di; Wegert, Sandara; Porreca, Frank; Lee, David K. H.
CS Allelix Biopharmaceuticals Inc., Mississauga, Can.
SO J. Pharmacol. Exp. Ther., (1999), 289(3), 1271-1276
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
CC 1-11 (Pharmacology)
AB There is growing evidence that nerve growth factor (NGF) may function as a mediator of persistent pain states. We have identified a novel nonpeptidic mol., ALE-0540, that inhibits the binding of NGF to tyrosine kinase (Trk) A or both p75 and TrkA (IC50 5.88.+-.1.87 .mu.M, 3.72.+-.1.3 .mu.M, resp.), as well as signal transduction and biol. responses mediated by TrkA receptors. ALE-0540 was tested in models of neuropathic pain and thermally-induced inflammatory pain, using two routes of administration, a systemic i.p. and a spinal intrathecal (i.t.) route. Morphine was also tested for comparison in the antiallodynia model using mech. stimuli. We show that either i.p. or i.t. administration of ALE-0540 in rats produced antiallodynia in the L5/L6 ligation model of neuropathic pain. The calcd. A50 values (and 95% confidence intervals) for ALE-0540 administered i.p. and i.t. were 38 (17.5-83) mg/kg and 34.6 (17.3-69.4) .mu.g, resp. ALE-0540 given i.t., at doses of 30 and 60 .mu.g, also blocked tactile allodynia in the thermal sensitization model. Although morphine displayed greater potency [A50 value of 7.1 (5.6-8.8) mg/kg] than ALE-0540 in anti-allodynic effect when given i.p. to L5/L6-ligated rats, it was not active when administered i.t. These data suggest that a blockade of NGF bioactivity using a NGF receptor antagonist is capable of blocking neuropathic and inflammatory pain and further support the hypothesis that NGF is involved in signaling pathways assocd. with these pain states. ALE-0540 represents a nonpeptidic small mol. which can be used to examine mechanisms leading to the development of agents for the treatment of pain.
ST ALE 0540 antiallodynia nerve growth factor
IT Skin, disease
(allodynia; characterization of antiallodynic actions of ALE-0540, a novel nerve growth factor receptor antagonist, in the rat)
IT Analgesics
(characterization of antiallodynic actions of ALE-0540, a novel nerve growth factor receptor antagonist, in the rat)
IT Nerve growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(characterization of antiallodynic actions of ALE-0540, a novel nerve growth factor receptor antagonist, in the rat)
IT 234779-34-1, ALE 0540
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of antiallodynic actions of ALE-0540, a novel nerve growth factor receptor antagonist, in the rat)
IT 9061-61-4, Nerve growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(characterization of antiallodynic actions of ALE-0540, a novel nerve growth factor receptor antagonist, in the rat)
RE.CNT 40
(1) Aloe, L; Arthritis Rheumat 1992, V35, P351 MEDLINE
(2) Andreev, N; Pain 1995, V63, P109 CAPLUS
(3) Averill, S; Eur J Neurosci 1995, V7, P1484 MEDLINE

(4) Chaplan, S; J Neurosci Methods 1994, V53, P55 MEDLINE
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6 ANSWER 1 OF 6 MEDLINE
AN 2001453684 MEDLINE
DN 21376296 PubMed ID: 11483654
TI The binding of zinc and copper ions to nerve growth factor is differentially affected by pH: implications for cerebral acidosis.
AU Ross G M; Shamovsky I L; Woo S B; Post J I; Vrkljan P N; Lawrance G; Solc M; **Dostaler S M**; Neet K E; Riopelle R J
CS Department of Physiology, Queen's University, Kingston, Ontario, Canada.. rossg@post.queensu.ca
NC NS36700 (NINDS)
SO JOURNAL OF NEUROCHEMISTRY, (2001 Aug) 78 (3) 515-23.
Journal code: JAV; 2985190R. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010814
Last Updated on STN: 20010903
Entered Medline: 20010830
AB It has recently been shown that transition metal cations Zn2+ and Cu2+ bind to histidine residues of nerve growth factor (**NGF**) and other neurotrophins (a family of proteins important for neuronal survival) leading to their inactivation. Experimental data and theoretical considerations indicate that transition metal cations may destabilize the ionic form of histidine residues within proteins, thereby decreasing their pK(a) values. Because the release of transition metal cations and acidification of the local environment represent important events associated with brain injury, the ability of Zn2+ and Cu2+ to bind to neurotrophins in acidic conditions may alter neuronal death following stroke or as a result of traumatic injury. To test the hypothesis that metal ion binding to neurotrophins is influenced by pH, the effects of Zn2+ and Cu2+ on **NGF** conformation, receptor binding and **NGF** tyrosine kinase (trkA) receptor signal transduction were examined under conditions mimicking cerebral acidosis (pH range 5.5-7.4). The inhibitory effect of Zn2+ on biological activities of **NGF** is lost under acidic conditions. Conversely, the binding of Cu2+ to **NGF** is relatively independent of pH changes within the studied range. These data demonstrate that Cu2+ has greater binding affinity to **NGF** than Zn2+ at reduced pH, consistent with the higher affinity of Cu2+ for histidine residues. These findings suggest that cerebral acidosis associated with stroke or traumatic brain injury could neutralize the Zn2+-mediated inactivation of **NGF**, whereas corresponding pH changes would have little or no influence on the inhibitory effects of Cu2+. The importance of His84 of **NGF** for transition metal cation binding is demonstrated, confirming the involvement of this residue in metal ion coordination.

L6 ANSWER 2 OF 6 MEDLINE
AN 1998424078 MEDLINE
DN 98424078 PubMed ID: 9753156
TI Reciprocal modulation of TrkA and p75NTR affinity states is mediated by direct receptor interactions.
AU Ross G M; Shamovsky I L; Lawrance G; Solc M; **Dostaler S M**; Weaver D F; Riopelle R J
CS Department of Medicine, Kingston General Hospital, Ontario, Canada.
SO EUROPEAN JOURNAL OF NEUROSCIENCE, (1998 Mar) 10 (3) 890-8.
Journal code: BYG; 8918110. ISSN: 0953-816X.
CY France
DT Journal; Article; (JOURNAL ARTICLE)

09758917

LA English
FS Priority Journals
EM 199810
ED Entered STN: 19981029
Last Updated on STN: 20000303
Entered Medline: 19981022
AB Equilibrium binding of 125I-nerve growth factor (125I-**NGF**) to cells coexpressing the tyrosine kinase receptor A (TrkA) and common neurotrophin receptor (p75NTR), cells coexpressing both receptors where p75NTR is occupied, and cells expressing only p75NTR, revealed reciprocal modulation of receptor affinity states. Analysis of receptor affinity states in PC12 cells, PC12 cells in the presence of brain-derived neurotrophic factor (BDNF), and PC12nnr5 cells suggested that liganded and unliganded p75NTR induce a higher affinity state within TrkA, while TrkA induces a lower affinity state within p75NTR. These data are consistent with receptor allosterism, and prompted a search for TrkA/p75NTR complexes in the absence of **NGF**. Chemical crosslinking studies revealed high molecular weight receptor complexes that specifically bound 125I-**NGF**, and were immunoprecipitated by antibodies to both receptors. The heteroreceptor complex of TrkA and p75NTR alters conformation and/or dissociates in the presence of **NGF**, as indicated by the ability of low concentrations of **NGF** to prevent heteroreceptor crosslinking. These data suggest a new model of receptor interaction, whereby structural changes within a heteroreceptor complex are induced by ligand binding.

L6 ANSWER 3 OF 6 MEDLINE
AN 1998264336 MEDLINE
DN 98264336 PubMed ID: 9603197
TI Effects of a peptide analogue of the amphiphilic domain of the common neurotrophin receptor on nerve growth factor-mediated motility of human neuroblastoma cells.
AU Wang W; **Dostaler S M**; Lawrence G; Ross G M; Riopelle R J; Dow K E
CS Department of Pediatrics, Queen's University, Kingston, Ontario, Canada.
SO JOURNAL OF NEUROCHEMISTRY, (1998 Jun) 70 (6) 2327-35.
Journal code: JAV; 2985190R. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
ED Entered STN: 19980618
Last Updated on STN: 20000303
Entered Medline: 19980605
AB Exposure of human neuroblastoma cells (IMR-32) to a peptide mimic of the cytoplasmic amphiphilic domain of the common neurotrophin receptor (p75NTR 367-379) resulted in enhanced nerve growth factor (**NGF**)-mediated inhibition of cell invasion in vitro. The peptide also enhanced **NGF**-mediated neurite extension and GAP-43 gene expression but had no effect on **NGF**-mediated cell survival. These latter functional effects mimicked influences on **NGF**-mediated neurite growth in other trkA-positive cells as reported previously. **NGF**-dependent trkA phosphorylation was significantly enhanced by the presence of the peptide, whereas high-affinity binding of 125I-**NGF**, both **NGF** receptors mRNA and protein expression, and trkA dimer/monomer ratios were not influenced. The studies suggest that ligand-mediated trkA activation has differential effects on cell motility phenomena and that the amphiphilic domain of p75NTR has a role in this differential signaling.

L6 ANSWER 4 OF 6 MEDLINE
AN 97398380 MEDLINE
DN 97398380 PubMed ID: 9256278
TI Zinc alters conformation and inhibits biological activities of nerve growth factor and related neurotrophins.
AU Ross G M; Shamovsky I L; Lawrance G; Solc M; **Dostaler S M**; Jimmo S L; Weaver D F; Riopelle R J
CS Department of Medicine, KGH, Queen's University, Kingston, Ontario, Canada.
SO NATURE MEDICINE, (1997 Aug) 3 (8) 872-8.
Journal code: CG5; 9502015. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
ED Entered STN: 19970916
Last Updated on STN: 20000303
Entered Medline: 19970902
AB A role for Zn2+ in a variety of neurological conditions such as stroke, epilepsy and Alzheimer's disease has been postulated. In many instances, susceptible neurons are located in regions rich in Zn2+ where nerve growth factor (**NGF**) levels rise as a result of insult. Although the interaction of Zn2+ with this neurotrophin has previously been suggested, the direct actions of the ion on **NGF** function have not been explored. Molecular modeling studies predict that Zn2+ binding to **NGF** will induce structural changes within domains of this neurotrophin that participate in the recognition of TrkA and p75NTR. We demonstrate here that Zn2+ alters the conformation of **NGF**, rendering it unable to bind to p75NTR or TrkA receptors or to activate signal transduction pathways and biological outcomes normally induced by this protein. Similar actions of Zn2+ are also observed with other members of the **NGF** family, suggesting a modulatory role for this metal ion in neurotrophin function.

L6 ANSWER 5 OF 6 MEDLINE
AN 96325528 MEDLINE
DN 96325528 PubMed ID: 8743735
TI Characterization of a distinctive motif of the low molecular weight neurotrophin receptor that modulates **NGF**-mediated neurite growth.
AU **Dostaler S M**; Ross G M; Myers S M; Weaver D F; Ananthanarayanan V; Riopelle R J
CS Department of Medicine, Queen's University, Kingston, Ontario, Canada K7L 2V7.
SO EUROPEAN JOURNAL OF NEUROSCIENCE, (1996 May) 8 (5) 870-9.
Journal code: BYG; 8918110. ISSN: 0953-816X.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199611
ED Entered STN: 19961219
Last Updated on STN: 20000303
Entered Medline: 19961106
AB The cytoplasmic region of the common neurotrophin receptor (p75(NGFR)) (rat, human, chick) contains a putative membrane-associating domain implicated in intracellular signalling. A peptide (R3) identical to this domain (p75(NGFR) 367-379) and various analogues of this peptide displayed

circular dichroism spectra in aqueous and non-polar environments identical to the amphiphilic tetradecapeptide mastoparan (MP) and were internalized by PC12 rat pheochromocytoma cells. The R3 peptide enhanced neurite growth in PC12 cells, embryo chick primary sensory neurons and fetal rat primary sensory neurons in vitro in the presence of sub-saturating concentrations of **NGF**. Peptide analogues of R3 not faithful to the distance and angular relationships of ionic groups and the putative amphiphilic structure of p75(NGFR)367-379 displayed reduced potency to enhance p75(NGFR) (PC12(nnr5)), had no influence on neurite growth. The R3 peptide had no effects on cell survival, cell binding or uptake of [125] **NGF**, affinity cross-linking of [125]**NGF** to p75(NGFR) or trkA monomers and homodimers, of **NGF**-mediated trkA monomer tyrosine phosphorylation. The studies implicate a role for a highly conserved motif of p75(NGFR) in the downstream modulation of **NGF** -mediated neurite growth.

L6 ANSWER 6 OF 6 MEDLINE
AN 95078246 MEDLINE
DN 95078246 PubMed ID: 7986806
TI Putative cytoplasmic amphiphilic domains in the nerve growth factor/tumour necrosis factor receptor superfamily.
AU Myers S M; Ross G M; **Dostaler S M**; Anderson M N; Weaver D F; Riopelle R J
CS Department of Medicine, Queen's University, Kingston, Ont., Canada.
SO BIOCHIMICA ET BIOPHYSICA ACTA, (1994 Nov 23) 1196 (1) 21-8.
Journal code: A0W; 0217513. ISSN: 0006-3002.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199501
ED Entered STN: 19950124
Last Updated on STN: 19950124
Entered Medline: 19950112
AB Potential alpha-helical regions in cytoplasmic domains of the **NGF** /TNF receptor superfamily were searched to identify amphiphilic sequences favouring association with membrane surfaces, analogous to the predicted secondary structure of mastoparan (MP). Similar to MP, NGFR (rat, chick, human), human TNFR-1, and human 4-1BB have domains with putative surface membrane associating sequences. The circular dichroism spectra of mastoparan and a peptide homologous to the putative amphiphilic domain of NGFR were identical in an aqueous milieu, and both adopted an alpha-helical conformation in trifluoroethanol.

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FILE 'REGISTRY' ENTERED AT 12:55:21 ON 05 JAN 2002
E ALE-0540/CN
L1 1 S E1

FILE 'BEILSTEIN' ENTERED AT 12:59:02 ON 05 JAN 2002
L2 0 S L1

FILE 'REGISTRY' ENTERED AT 12:59:20 ON 05 JAN 2002
L3 1 S L1

FILE 'MEDLINE' ENTERED AT 13:01:44 ON 05 JAN 2002

09758917

L4	1	S ALE 0540
		E DOSTLER S/AU
		E DOSTALER S/AU
L5	7	S E3-E4
L6	6	S L5 AND NGF